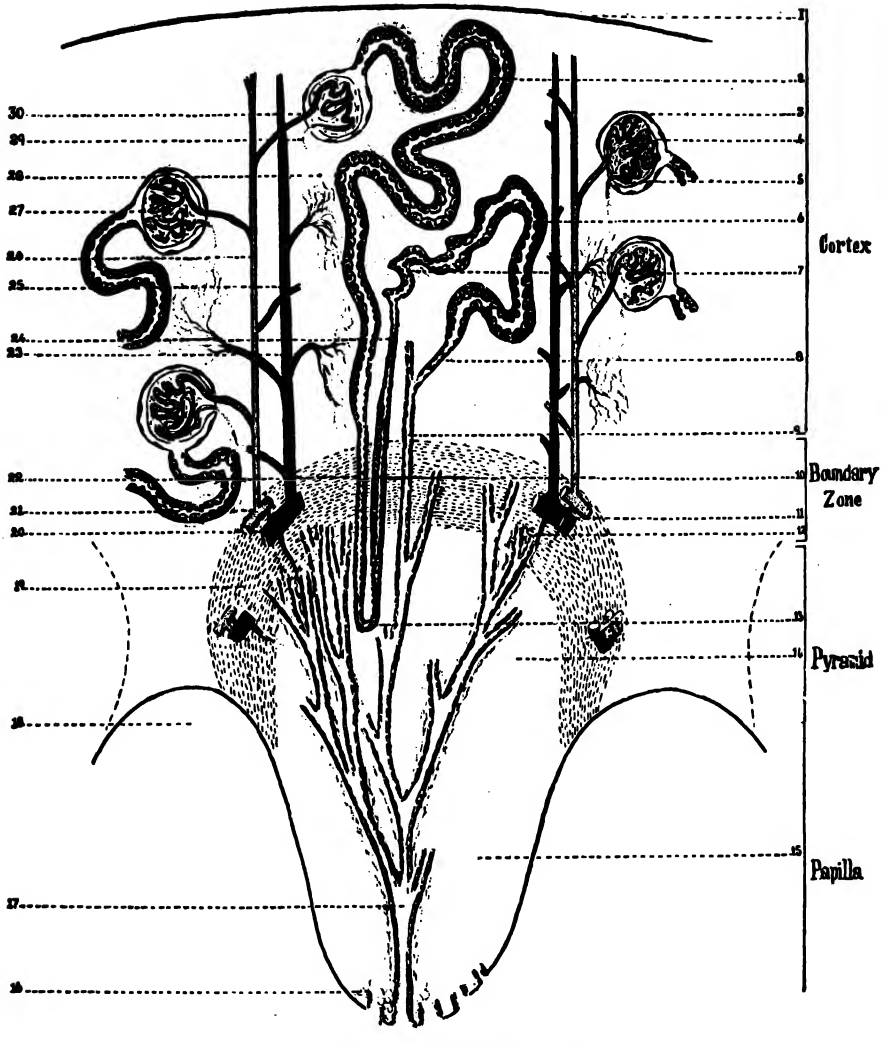
PLATE I.



STRUCTURES OF THE NORMAL KIDNEY.

1, Capsule; 2, convoluted tubule; 3, outer layer of the capsule; 4, intervening space; 5, reflected portion of the capsule; 6, distal convoluted tubule; 7, irregular portion of distal convoluted tubule; 8, end portion of distal convoluted tubule; 9, collecting tubule; 10, ascending loop of Henle; 11, arteria recta; 12, vena recta; 13, loop of Henle; 14, pyramid; 15, papilla; 16, papillary vascular plexus; 17, main collecting tubule; 18, calix; 19, boundary zone; 20, larger branch of renal vein; 21, larger branch of renal artery; 22, descending loop of Henle; 23, interlobular vein, collecting from the stellate plexus; 24, narrow portion of ascending loop of Henle; 25, interlobular vein; 26, interlobular artery; 27, glomerular capillary network; 28, stellate plexus of capillaries; 29, efferent vessel; 30, afferent vessel.

THE ANATOMIC HISTOLOGICAL PROCESSES OF BRIGHT'S DISEASE

AND THEIR RELATION TO THE FUNCTIONAL CHANGES

LECTURES DELIVERED IN THE

RUSSELL SAGE INSTITUTE OF PATHOLOGY

CITY HOSPITAL, NEW YORK

DURING THE WINTER OF 1909

BY

HORST OERTEL

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ILLUSTRATED

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1910

PRINTED IN AMERICA

TO

EDWARD G. JANEWAY

TO WHOM THE SCIENTIFIC PRACTICE OF MEDICINE IN AMERICA
OWES A HEAVY DEBT, AND WHOSE METHODS, WORK
AND ACCOMPLISHMENTS HAVE AT ALL TIMES
BEEN EXAMPLE, AID, AND INSPIRA-
TION, IN LASTING GRATITUDE

PREFACE

THESE lectures were delivered at the request of the Resident Staff of the New York City Hospital in the Russell Sage Institute of Pathology, during the winter semester 1908 to 1909 before an audience of recent graduates and some advanced undergraduates in medicine. My hearers wished to obtain in systematic and connected form the almost daily experience in hospital and pathological institute. They wanted primarily to intelligently understand what they saw at the bedside and at the autopsy table.

The lectures deal, therefore, with the morphology of nephritis, and in a somewhat different form from the usual manner. Everywhere I have endeavored to particularly emphasize relations and to reconstruct the whole as a unit of interwoven processes, rather than a mere statement of facts. As this method of treatment may not be unwelcome to a wider medical public and, as far as I know, does not exist in English literature, I now publish them practically in the form of the stenographic report, except for some additions and explanatory notes. This accounts for an unevenness of treatment and some local coloring in the presented material.

I may, perhaps, be pardoned if I qualify here my stand in teaching medicine and particularly pathology in some detail. The average American medical student of the present day is taught in his college a large variety of medical subjects, but in a

manner which, according to my experience, is not apt to develop in him a plastic, living and flexible conception in any subject, in other words, no independent thought. Forced by a rigid, prescribed schedule, which leaves him no academic freedom, individual responsibility and time for thoroughness, he memorizes, mostly from text books, lectures and recitations, and disconnected demonstrations and clinics many statements and some facts. His conceptions are those of a certain text-book, of a certain page, or, similarly, of notes of a certain instructor. They are, if the term is permissible, fossilized and immovable. The ability derived from personal, well directed experience under an instructor, the ability to form plastic pictures of occurrences which enable one to combine visual and live, true ideas of pathological processes without becoming unreliable and phantastic, are foreign to most of our present medical generation. Thus, our present methods of teaching resemble the dead inflexible formalism of the scholastic period taught in the European universities during the middle ages.

The medical graduate of to-day enters a hospital, faces life and meets the keenest disappointment. His hard and fast text-book lines and schoolboy classifications, memorized carefully for recitation and written examinations, are broken and shattered. But worse, having no other foundation, no critical judgment of relative values, which is derived from historical knowledge of a science, he is unable to utilize his new experience. He holds new parts of a chain, but cannot unite them, much less link them to the old. It takes a strong mind, much stronger than the average medical graduate has, to evolve successfully out of these complicated circumstances. The others are simply content to again memorize actual experience in the Hospital, and apply it as well as they can. They remain uncultured.

Herein lies a deficiency of our system of instruction. "Die Welt des Sehenden," I have heard Wundt impressively say in one of his lectures, when I was a student in Leipzig, "ist die der Gesichtsvorstellungen." This view of the great psychologist is amply followed in all European universities. Medical teaching is primarily directed toward developing the power of objective observation and a scientific method of thinking. Instruction is given not outside of the hospital, but in the hospitals and in the autopsy rooms where things can be seen, with much personal freedom in work and study. Nothing is more important in the education of a physician than the development of clear visual, anatomical ideas of diseased processes and ability to construct their possible relations. The importance of this "anatomical idea" in the education of the physician was constantly emphasized by Charcot and Virchow.

It is to be regretted, therefore, that unfortunate circumstances still make it impossible to conduct most of our large hospitals as academic institutions.

But I also view with some fear for our future in medical education the present tendency in some of our medical colleges to introduce specialized branches of pathology, medicine and surgery into their undergraduate courses at the expense of the morphological discipline, instead of a greater effort to properly develop the opportunities of the latter in its relation to clinical medicine. I would not deny their value. Indeed experimental pathology, medicine and surgery are very necessary supplements or better complements of morphology for the elucidation of special problems and in the hands of experienced pathological anatomists; they are suited particularly for advanced students. But they can never replace that knowledge which is obtained from the study of a disease. The latter is an experiment of nature which develops out of ever-varying, complicated, external

and internal conditions which we cannot exactly artificially duplicate in causes, number, time and expressions.*

No less a brilliant experimental investigator and leader in experimental pathology than Cohnheim significantly delivered his own inaugural address in assuming the chair in general pathology in the University of Leipzig, "Ueber die Aufgaben der pathologischen Anatomie."

It is, indeed, a serious problem which confronts today, not only the general medical education of our younger generation of students, but that of the developing pathologists. Already a lack of thorough pathologic anatomical knowledge, experience and depth of thought becomes noticeable in much of the recent pathological literature on the part of many of those who have followed a one-sided and more spectacular specialization in pathological research without sound anatomical foundation. Those who doubt my words should read the warning of Orth in that matter, "Zur Bezeichnung der bösartigen epithelialen Neubildungen." Zentralblatt f. allg. Path. u. path. anat., 11, 1908, and v. Hansemann in Zeitschrift f. Krebsforschung, Vol. VII, 1909.

A spirit of anatomical renaissance, therefore, permeates these lectures. But I have also endeavored to emphasize what Cohnheim in his inaugural address said of pathological anatomy as contrasted with normal anatomy: "Die pathologische Anatomie ist gar nicht eine deskriptive Wisenschaft in dem Sinne wie es die normale ist." Pathological anatomy is an explanatory discipline. Its educational value is therefore twofold: It presents the visual picture of a process and it discloses the genesis

* Compare the concluding remarks of Marchand in the description of the new pathological institute at Leipzig in the Festschrift for the 500th anniversary of the University. In Austria a very desirable separation of pathology into two chairs, pathological anatomy and experimental pathology, has already taken place; in Germany the latter is now taught by clinicians. The situation is very similar to the state of physiology and anatomy fifty years ago.

of the process, at least, prepares the proper way for its understanding. These points I had constantly before my eyes in the delivery of these lectures.

Some may find, perhaps, a more extensive review of elementary and general pathological questions than may seem warranted to them by the nature of the subject in a graduate course. After deliberation, I have concluded, however, not to eliminate them in the publication of these lectures, for the activity of investigators has been so productive that such reviews might possibly be welcome to those who have been unable to completely follow these subjects. Some of them have had important contributions since these lectures were ready for publication. Particularly in the doctrine of fat degeneration and fat infiltration, the views still undergo a kaleidoscopic change.

Many of the ideas expressed in the following pages are based on data collected by me and former and present assistants during a period of six years at the City Hospital. My greatest indebtedness is to Dr. Lindsay Milne, who has sacrificed much of his own time and thought, and to whom I owe the selection of typical pictures for the accompanying plates. They were executed by Mr. Martin, the artist of the Russell Sage Institute. The generosity of the Trustees of the Russell Sage Institute made the publication possible. To the publishers I owe very hearty coöperation and valuable suggestions.

I may fittingly introduce these lectures after the manner of Morgagni in his great "De sedibus et causis morborum per anatomem indagatis:" Crassus in Cicero, "De oratore," II, 6. 25, quotes Lucilius as follows: "C. Lucilius, homo et doctus et perurbanus dicere solebat *neque se ab indoctissimis neque a doctissimis legi velle, quod alteri nihil intellegerent, alteri plus fortasse quam ipse.*" "C. Lucilius, a learned and very polished

man was in the habit of saying *that he did not wish to be read either by the very learned nor by the very uneducated; for the latter would not understand him, while the former might possibly know more than he himself did.*"

HORST OERTEL.

RUSSELL SAGE INSTITUTE OF PATHOLOGY, CITY HOSPITAL,
NEW YORK CITY, *November, 1910.*

CONTENTS

THE ANATOMIC HISTOLOGICAL PROCESSES OF BRIGHT'S DISEASE

FIRST LECTURE*

Historical Introduction and Classification

Gentlemen:

It is with great pleasure that I have followed your invitation to speak to you about the diseases of the kidney ordinarily grouped as Bright's disease. But I appreciate, and I think you probably will before I finish these lectures, the great difficulties which present themselves in a study of renal lesions, and more particularly in that group which we intend to discuss.

The diseases of the kidney differ in a peculiar way from the diseases of other organs. Three points enter into this.

First, there exists an exceptional, intimate correlation of the diseases of the kidney with concomitant or associated conditions which we cannot dismiss from our consideration as we do in the study of other organs. To illustrate this concretely I may say that one can investigate the inflammations of the lung, of the heart, of the liver, or of the spleen, more or less independently of other organs. We can abstract them from the rest of the body, so to speak, and observe them independently. This is hardly possible, however, in the diseases of the kidney, more especially in Bright's disease. I need only to remind you that

* Delivered on January 14, 1909.

the questions of hypertrophy of the heart, of œdema, of circulatory disturbances, of changes in the blood-vessels, of albuminuria, etc., are so intimately connected with the changes in the kidneys that it becomes evident at once that herein lies a considerably complicating factor.

Secondly, there exists great difficulty, and at the same time a much greater necessity here than in almost any other organ, in establishing a proper relationship between structural and functional changes. But not only are we almost entirely ignorant, or at least uncertain, of many of the physiological conditions of the secretion and of the part played therein by the various components of the kidney, but in the pathological variations we are constantly confronted by obstacles which consequently are hard or even impossible to overcome.

Finally, a third factor which conflicts, and a rather personal one, is the multitude of views held with regard to the normal and pathological functions and the anatomical and histological changes in the kidney, which, on account of their number and of the peculiar subjective tendency here displayed, make it almost impossible to present them satisfactorily and entirely.

It is by reason of these conflicting opinions that the presentation of the subject is difficult, and it will undoubtedly plainly appear when I review for you in a necessarily short and circumscribed way the evolution of the various conceptions of the character of Bright's disease. To a great extent this is responsible for the uncertainty which exists even to-day.

This leads me to qualify the necessity of such a historical review. It is, no doubt, interesting and instructive to follow the historical development of the various views held about any disease; but I consider it imperative in the diseases of the kidney, because it is impossible to have an appreciation of the relative value of the present ideas, unless we are fully acquainted with

the origin of these ideas and the developments through which they have passed.

It appears that there are essentially three interwoven, disputed points, and, as you will see, fundamental ones. The first is, What inflammations of the kidney are to be included under the heading of Bright's disease? The second, What are the characteristic features of this inflammation? The third, Are there any non-inflammatory processes which form essential parts of this disease?

Of them, I consider the second the most important. It is easy for you to appreciate that whatever conception may be held of an inflammatory condition of the kidney is necessarily dependent upon the view one has of inflammation in general; and the various views which have been advanced from time to time center around the evolution of this general pathological conception.

One mistake, too frequently made as the result of histological studies, is to regard pathological processes as stationary, inflexible, of great uniformity in appearance, or at least going on with mathematical precision in temporary arrangement. One ought to appreciate from the start that, as the name implies, pathological processes are processes; that is, forever changing. Histologically we observe stages of a process, but we cannot interpret them in the sense of a simple introduction of certain abnormalities into an organ, where they lie more or less like foreign bodies. Necessarily, they continually vary, constantly influenced by conditions which again depend upon a large number of outside factors and an equally large number of ever-changing individual reactions on the part of the organism. Strictly speaking, one might say that there are as many diseases as there are diseased individuals. While this is to be taken into consideration in the study of any disease, it can much less be dis-

regarded in nephritis. Diseases must be grouped, therefore, with a thorough appreciation of these possible variations, and the stricter and more circumscribed a classification, the more faulty it will always be. For a definition, to be exact and exhaustive, must consist in a repetition of all component parts of a substance or a process. These it sets out to systematize. Thus, as Taine has put it, "un systeme est une explication de l'ensemble et indique une oeuvre faite." Diseases live, however, constantly change, and develop. Influenced by innumerable outside and inside conditions, they defy strict codification in much the same manner that any form of life does.

Guided by such considerations, I shall not follow the plan frequently employed by lecturers in a too dogmatic and complete presentation of the subject. It will be my endeavor to present essentially the certain anatomical and histological knowledge which has gradually accumulated in the course of time, and which constitutes the fundament of the whole structure. I shall treat these changes in their general genesis and relation to each other and to the associated functional disturbances. Thus, although incomplete, it may serve you better for future thought and experience than a recital of many unconnected facts and ideas.

Diseases of the kidney have been known for a very long time; even the Bible mentions as important "to test a man's heart and kidneys," which may indicate a possible knowledge of the relationship between heart and kidneys; but reliable data do not appear until more thorough knowledge, gained by autopsies of human beings, drew attention to certain anatomical changes which the kidney may undergo. Ætius, between 300–400 A.D., came to the conclusion that certain cases of œdema and anasarca were associated with hardened kidneys. This knowledge was extended on the clinical side by an equally good observer,

Avicenna, about 1000, who found that in a certain number of these cases the urine was thin, watery and increased in quantity.[1] But it was more especially Morgagni,[2] during the latter half of the eighteenth century, whom we properly regard as the founder of pathological anatomy, who described with great care, clinically and anatomically, cases of granular, contracted kidneys, associated with dropsy. In certain other observations which he made in order to determine the cause of dropsies he found healthy kidneys but distinctly diseased livers. Dropsies, which were then regarded as morbid entities, were therefore classified as with and without kidney disease. A great step toward better knowledge of the diseases of the kidney was made by Cotugno in 1770,[3] who demonstrated for the first time the occurrence of serum-albumin in the urine of dropsical patients. He brought that fact into proper relation with cases of œdema and anasarca, but erroneously held that it represented an effort on the part of the organism to get rid of the œdematous fluid.

Cruikshank[4] elaborated Cotugno's findings, and found that certain cases of œdema showed no albumin in the urine; finally Wells[5] demonstrated the presence of blood and albumin in the urine of scarlet fever. Gradually, then, positive anatomical and clinical evidence accumulated, which pointed more or less closely to the connection of dropsy, albumin in the urine, and kidney disease. Early in the last century the examination of urine had been well elaborated, particularly by Brande and Scudamore,[6] who already knew that albuminous urine contained less urea than did normal urine.

Bright's work was ushered in by that preliminary knowledge. Like his predecessors, he commenced his observations with an investigation into the causes of dropsy, and it was his purpose to determine the underlying anatomical condition. He collected and grouped, very excellently indeed, a certain number of cases

of œdema associated with changes in the kidney, and in a similar fashion certain cases of ascites, anasarca, or œdema with diseases of the liver, and it is mainly Bright's credit to have pointed out more clearly than any one before him that certain cases of dropsy are constantly associated with certain changes in the kidneys, and others equally with certain diseases of the liver. These first observations appeared in 1827—a classical publication illustrating the great value of thorough, painstaking, objective observations and deductions therefrom.[7] It may be said that almost everything which Bright advanced, as far as pure observation goes, has stood the test of time until to-day. The clinical pictures which he presented, particularly later, in the first volume of the Guy's Hospital report on chronic renal disease, have never been better drawn by any later author, and to-day we have no better description than that he gave us.[8] Even on the anatomical side his observations stand to a great extent to-day. He properly correlated the hypertrophy of the left ventricle of the heart with some diseases of the kidney, and he advanced the same views with regard to this relation which are held to-day. (Particular attention ought to be paid to the execution of the plates accompanying his first report of medical cases in 1827, and printed in London, showing the excellent workmanship of that time.)

Bright did not, of course, finish his work with this original account, but subsequently, in the Guy's Hospital Reports, he published a number of very important observations, extending his original views on the subject. He divided the disease into three groups:

"In the first the kidney is apparently in a stage of degeneration, causing this organ to be less firm, yellow, mottled. This may lead to an alteration characterized by a tuberous appearance of the surface.

"In the second, the kidney is transformed into a granulated texture, as if fine grains of sand had been sprinkled over it, and sometimes innumerable specks, of no definite form, are equally strewn over the surface. Later, the kidney assumes a tuberous appearance, as in stage one.

"In the third, the kidney is quite rough, with numerous pin-point projections, yellow red and purplish. It is hard, lobulated, almost cartilaginous, and contracted."

In these lesions just quoted we can recognize those which are termed to-day acute nephritis, chronic parenchymatous nephritis, and contracted kidney.

I must now touch upon an important point, which you must well remember, as it is one which subsequently has caused a great deal of discussion. Bright, from the start, held that all these three stages were of uniform character, in the sense that one advanced to the other; that all, then, stood in temporary relation to each other. He regarded the changes "as due to alterations in the circulations of the kidney, brought about by influences of the skin and stomach, *or producing a decidedly inflammatory condition of the kidney.*"* Bright did not think that the lesions here presented were the only ones which were found in the kidney, for he described in his original article several others, which, however, were regarded as of minor importance.

The ideas of Bright necessarily attracted attention, primarily in England, and were taken up particularly by Christison, Osborne and Gregory.[9] Christison separated the disease into acute and chronic forms, although he held that it was essentially chronic. He doubted that all the various lesions were stages of one morbid process, but left the exact nature of it undetermined. He described the following seven different changes in the kidneys:

* I particularly quote this statement of Bright's, as Leyden states that the idea of inflammation had not been expressed by Bright, but introduced by Reinhardt and Frerichs. An evident mistake!

1. A congestion of the kidneys with or without granular deposits in the substance.

2. True granular degeneration of cortical or tubular structure. (*a*) Finely granular, (*b*) botryoidal.

3. Degeneration by a smooth, homogeneous, yellowish-gray mass, intermediate in consistence between that of the liver and the brain.

4. Disseminated tubercles.

5. Induration of semi-cartilaginous hardness.

6. Atrophy with disappearance of proper renal structure and with or without one of the previous morbid states.

7. Simple anæmia.

He recognized these in the following stages: Incipient stage of congestion, or reaction. Middle stage with a nearly destroyed cortex. Advanced stage, where the tubular masses were destroyed.

Christison knew that the disease tends to suppress the solids in the urine, that it is frequently associated with serous inflammations and severe anæmia, and emphasized the impregnation of the body-fluids with urea.

On the other hand, some opposition arose on the part of Graves, Elliotson,[10] and Copland.[11] Graves,[12] particularly, regarded the kidney lesions, not as the cause of œdema, but as the result, believing that the changes in the kidney were secondary to an effort to remove the œdematous fluid from the body.

Further observations were made by Willis,[13] who was the first to draw attention to the fact that albuminous urine occurred in a number of other conditions than had been previously recognized.

From England the knowledge of this group of diseases spread to France, and was particularly taken up by Rayer[14] and his pupils, Tissot,[15] Sabatier,[16] Desir,[17] and Genest.[18] Rayer pub-

lished an extensive valuable monograph, presenting a rich material of good observations, concluding that Bright's disease was an inflammatory condition of the kidney, essentially characterized by an albuminous urine, containing less salts and urea than the normal and always associated with œdema. He sharply differentiated it from other forms of inflammation which he grouped as rheumatic nephritis.

An entirely different start in this study was made by Solon.[19] He collected all cases of "albuminuria," a term introduced by him, and tried to arrive at some conclusion from the material thus collected. But inasmuch as he necessarily included in this group cases of all sorts, some of which could not have even been kidney diseases, he did not arrive at any definite, valuable conclusion. His controversy with Rayer did not clear the matter any. Solon made the observation, however, that the symptoms of granular kidney frequently differ from the others, particularly in an absence of œdema, but were associated with nausea, vomiting, and pain.

The earliest histological investigations into Bright's disease were made in Germany by Gluge, Valentin, and Hecht, after Becquerel[20] in France had explained Bright's disease as a hypertrophy of Malpighian corpuscles, which he regarded as the secreting structures of the kidney. But because of a very insufficient and somewhat hypothetical conception of the finer structures of the kidney, they proved of little consequence. Gluge[21] regarded it as inflammation, as he discovered his "characteristic inflammatory globules," and Valentin[22] as a disease of the blood, being unable to find any characteristic changes in the kidney, and Hecht,[23] finally, as a degeneration, analogous to his opinion of cirrhosis of the liver. Gluge described later three forms of the disease. First, one of inflammation; second, a cirrhosis, which he meant in a literal sense, as deposits of fat; third, an "uncer-

tain" degeneration. As you see, an unsatisfactory, deficient classification!

The great anatomist Henle[24] was the first to give a comprehensive, reliable description of the histology, and a great many of his histological and anatomical descriptions are considered correct, even at the present day. He regarded the whole process as an exudation of fibrin between, and into, the tubules, which organizes, contracts, and produces a cirrhosis of the kidney. He employed the term cirrhosis in the modern sense of connective-tissue formation with contraction. Based on his own observations and those of others, he differentiated between these types:

1. Steatosis of the kidney (Gluge and Johnson).
2. Subacute inflammation with cyst formation.
3. Cirrhosis of the kidney.
4. Swelling of the kidney due to œdematous infiltration and first stage of cirrhosis.
5. Acute desquamative nephritis following exanthemata (Johnson).

The glomeruli, in his opinion, were not changed. He should be particularly remembered as being the first to give a careful description of tube casts, later studied thoroughly by Nasse, Simon, Scherer, and Rovida. He held that they were composed of fibrinous exudate, and similar views were entertained by Vogel.

On the other hand, Canstatt,[25] who with Siebold had studied two cases of the disease, regarded the lesions as either a non-inflammatory deposit of albuminous fibrinous granules, or of fat in the cortex: a "steatosis renum."

In England there appeared about this time Bowman's great work on the finer structures of the kidney, which gave a new impetus to the study of Bright's disease. Of these works, those of Johnson,[26] Toynbee,[27] Simon,[28] and Busk[29] are of especial importance. In these investigations there appears for

the first time an endeavor to hold different processes responsible for the symptom-complex and characteristic features of Bright's disease.

Toynbee was the first to describe the thickening of the arteries, and interstitial cellular proliferation, while Johnson paid particular attention to the fatty infiltration of the tubular epithelium, leading to what he called a chronic desquamative nephritis. He held that this may develop independently without previous acute changes, and therefore was one of the first to discard the uniform view of Bright's disease. He recognized, further, amyloid and fatty kidney. Busk's idea was that the contracted kidney resulted from a capillary phlebitis, as granular liver results from a portal thrombo-phlebitis.

Important contributions appeared in works of Reinhardt[30] and Frerichs.[31] Reinhardt regarded the lesion as a *diffuse inflammation* with a peculiar lack of organization on the part of the fibrin, and leading to a destruction of the epithelium. Frerichs, extending these views, distinguished between the following absolutely correlated stages: First, hyperæmia and beginning exudation; second, exudation and metamorphosis of the exudate; third, regression and atrophy, in which the exudate may be partly transformed into connective tissue. This classification came into general use before Virchow. On the other hand, Rockitansky,[32] again separated exudative nephritis entirely from Bright's disease and regarded as characteristic of that lesion a degeneration and desquamation of the epithelium. But he allowed a possible combination of Bright's disease with nephritis.

We come now to a very important turning-point in the history of Bright's disease, as well as in the whole history of pathology. In 1852 Virchow[33] published a celebrated article in the fourth volume of his "Archives," on "Parenchymatous Inflammation."

He was the first to use this term, which since then has become common property. In it he laid the corner-stone for all future ideas about parenchymatous inflammation, although you will presently see that Virchow's ideas of parenchymatous inflammation are entirely different from what was later regarded as such. It may therefore be necessary to detail some of his views in that relation.

Before the time of Virchow, the ideas of inflammation may be gained from Vogel's definition: "Inflammation = capillary hyperæmia + hydrops fibrinosus." Virchow's observations led him to the conclusion that it was erroneous to regard the exudate as the essential features of any inflammation, but that the constant characteristic of inflammation was parenchymatous degeneration. This resulted from an excessive imbibition of exuded fluid, which he regarded as exaggerated nutritive material. It led him to the idea that the inflammatory process was really a nutritive disturbance of parenchyma cells, and he applied this view particularly to the kidneys. As the result of this excessive nutriment the cells become large and swollen, and the albuminous molecular contents are increased. Thus, he assumed, the protoplasm of the cell disintegrates and becomes fatty and granular. In some cases the whole of the exudate is thus consumed by the epithelial cell, so that the fibrin does not appear, and the only evidence of the presence of the exudate is found in the albumin which is carried off in the urine. Virchow, then, regarded the parenchymatous change as the essential feature of every inflammation, and this disturbance of nutrition, as he termed it, differs from simple degeneration only in degree. He concludes with these words: "I vindicate above all the degenerative character of inflammation, and although I regard it as increased nutritive phenomenon, I do not see in it an evidence of increased strength, but an expression of its diminution."

Guided by these considerations, he distinguished between three forms of nephritis, for which he created the following terms, which are still employed to-day, although, as you will appreciate, in a different sense from the one Virchow gave them.

First, catarrhal inflammation, where cells become granular, opaque, and break off the basement membrane.

Second, croupous inflammation. Here the cells show essentially the same changes, but become mixed with a coagulated fibrinous exudate.

Third, true parenchymatous inflammation, which is the most intense, and consists of a granular swelling and disintegration of cells with the formation of a soft detritus.

Niemann, one of Virchow's pupils, in his inaugural dissertation (1848), gives the following interesting and excellent description of the finer parenchymatous changes in nephritis in Virchow's sense: "Qui quiden processus (Infl. parenchymatosa) in renibus procedit, et quiden maxime in epithelii cellulis canaliculorum uriniferorum contortorum in substantia corticali. Epithelii cellulæ majores fiunt, *endosmosis aucta*,* eorumque contentum mobilum turbidumque fit. Cellulis autem amplificatis canaliculi uriniferi extenduntur et renum ambitus major existit. Canaliculorum amplificatione circuitus sanguinis in vasis capillaribus impeditur, unde anæmia renum oritur, in renum superficie astra venosa conspiciuntur, quia sanguis venosus refluere nequit.—Tum cellulæ illæ metamorphosin adiposam subeunt, emolliuntur, denique massam formant pultiformem, quæ urinæ admisceri potest, quo urina fit adiposa. Quæ quidem admixto raro fit, plerumque massa illa resorbetur. Processu progrediente canaliculi uriniferi collabuntur, quæ in renum superficia loca depressiora formantur et renes speciem granulosam præ se

* Italics mine.

ferunt. Loca elata in renum superficia colore intense flavo portes sunt, quæ metamorphosin adiposam non subierant."

He, therefore, classifies the lesion in the three previously detailed stages.* It is interesting to recall here that Virchow sharply differentiated the cicatricial formation as the result and not as part of the inflammatory process. We will learn that such a stand has only recently been taken again by Aschoff.

In 1859 Arnold Beer, a pupil of Virchow, stimulated by Bowman's and Goodsir's work, published a monograph on the connective tissue of the human kidney in health and disease.[34] In this he paid particular attention to the interstitial hyperplasias in various forms of nephritis, which he carefully described, alone and in connection with the accompanying vascular and parenchymatous changes. It is interesting to note, in view of Weigert's later work and ideas, that he inclines to the belief that atrophy of tubules and glomeruli precedes the connective-tissue hyperplasia, and that the process is more or less of a peculiar complementary character. (Pp. 119 and 122.) Interesting is, further, that he, as the first, attaches considerable significance to the proliferation of the epithelium in nephritis (p. 125), which explains, in his opinion, that kidneys may show microscopically small atrophic glomeruli and appear granular, but, at the same time, as a whole, are of normal size or even enlarged. The tubules in these cases appear dilated and filled with hyperplastic epithelium. Future investigations have unfortunately disregarded this important process of the lesion.

Beer was, therefore, the first to draw the interstitial connective-tissue changes prominently into the discussion. When it is further considered that shortly afterward appeared Cohnheim's[35] classic observations on inflammation, which again placed the essential features of that process in and around the vascular system,

* Cited after Virchow.

and which exerted a great influence on all contemporary investigators, it becomes appreciable how the attention centered once more around these changes. This influence is well shown in the works and efforts of Traube[36] to differentiate between a circumscapular and intertubular nephritis, and to neglect the parenchymatous involvement. The subsequent establishment of glomerulonephritis as a special type by Klebs,[37] and which was later regarded by Ribbert[38] as the universal incipient lesion of all forms of Bright's disease, brought equal support to the prominence of the vascular and interstitial changes.

However, it remains Traube's great merit to have conclusively separated the cyanotic and amyloid kidneys, as non-inflammatory, from nephritis.

These views of the purely vascular, interstitial inflammatory nature of nephritis did not entirely succeed in replacing Virchow's conceptions. As in other scientific discussions where both sides of an argument contain truth, both were accepted, but unfortunately as distinct and different types of nephritis, and it became prevalent to speak of parenchymatous and interstitial nephritis in a contrasting sense.

This created a very grave and fundamental error from which pathology is still suffering to-day. It was based entirely on the too narrow definitions of inflammation of Virchow on the one side, and of Cohnheim on the other.

It was Rosenstein[39] who first endeavored to establish a reconciliation between the two extreme views of parenchymatous and interstitial inflammation, inasmuch as he regarded epithelium as well as interstitial tissue involved. He, therefore, advocated the term and idea of diffuse nephritis, originally introduced by Reinhardt, and further emphasized that one should differentiate between degeneration and inflammation. Herein is expressed an actual change in the ideas of the character of inflammation, as

essentially represented by the earlier writers and also by Cohnheim and Virchow. Whereas these considered an inflammation only as an exudation, and Virchow essentially as a degeneration, Rosenstein intended to combine both as, not necessarily dependent, but correlated processes. The uncertainty, however, on all questions here discussed was particularly well shown in the discussion of Bright's disease at the first meeting of the German Congress for Internal Medicine in 1882, where Leyden,[40] for instance, held that all cases with albuminous urine and anasarca should be grouped as Bright's disease, while all others were to be regarded as nephritis. This, of course, included the non-inflammatory amyloid in the category of Bright's disease, while a contracted kidney without œdema and albumin was to be excluded. A perfectly untenable position!

In England, further studies gradually led away from the original ideas of Bright. After Christison and Johnson had doubted the intimate relationship of all forms of nephritis, voices in that direction became stronger. Particularly Samuel Wilks[41] regarded the large white kidney and small granular kidney as independent affections, followed by Grainger Stewart,[42] and in 1872 Gull and Sutton[43] went so far as to declare that arterial and capillary fibrosis was the cause of contracted kidneys.

In Germany, Bartels[44] was the first to introduce the idea of the independent character of the so-called chronic interstitial nephritis which he attributed to a primary growth of interstitial tissue. He distinguished it from the so-called parenchymatous form.

Senator,[45] however, again drew attention to the point that a sharp division between these so-called chronic parenchymatous and interstitial forms was not possible, and that one ought to speak, as Reinhardt and Rosenstein had done, of diffuse nephritis. At the same time, he admitted that there exists a

form of nephritis distinct from the ordinary interstitial type, in the arteriosclerotic kidney.

The modern turning-point in the subject of nephritis may be properly said to commence with the observations of Weigert,[46] which, like Virchow's, are important, not only from the standpoint of kidney pathology, but in a much more general sense. Weigert very strongly advocated a uniform view of all kidney lesions, and claimed that a sharp line between the various forms could not be drawn, and that they represented only quantitative differences. His most radical idea expressed, however, was that the interstitial inflammatory and productive changes are always secondary and caused by a parenchymatous destruction or loss. This idea, which has become widely adopted, is, as you appreciate, the very opposite of Virchow's conception. It marks the time when parenchymatous inflammation began to be regarded in an entirely different sense from that of the originator. Parenchymatous degeneration became no more a nutritive disturbance, but the result of an irritant, and the direct expression of its injury. It is this conception of parenchymatous degeneration which rules to-day.

While Weigert held this opposing view to Virchow, he nevertheless brought parenchymatous degeneration in a direct pathogenetic relation to the interstitial changes, and, as I shall have occasion to mention immediately, the present generation does not attach any more pathogenetic significance to these terms.

Weigert distinguished between four intimately correlated forms: Acute nephritis, characterized mainly by cellular exudate; the subchronic nephritis, characterized by beginning connective-tissue growth; the chronic nephritis, characterized by a beginning contraction; and, lastly, the granular atrophy, characterized by a very complete loss of parenchyma.

These ideas of Weigert were again strongly opposed, mainly by Ziegler,[47] Nauwerck,[48] Bartels,[49] and, to some degree, by Senator.[50]

Nauwerck, particularly, drew attention to the fact that the dependence of the interstitial changes on the parenchymatous destruction can by no means be always demonstrated.

Ziegler follows Weigert in so far as he also takes a uniform view of all hæmatogenous forms of nephritis, believing only in a graded and no essential difference. That it is possible to differentiate strictly between degenerations and inflammations is denied by Ziegler. In opposition to Weigert, following Bartels, he describes a primary interstitial nephritis, the result of a primary connective-tissue hyperplasia, leading to induration.

These views, opposing Weigert's conclusions, found further support in certain observations on the so-called acute interstitial nephritis, as first described by Biermer,[51] Ernst Wagner,[52] Klebs,[53] and lately, with particular care, by Councilman.[54] The latter regards this lesion as a *focal* infiltration by plasma cells, derived from emigrated lymphocytes; but this cannot find its explanation in a primary epithelial degeneration, which is always *diffuse*. When the latter, however, becomes intense, polynuclear leukocytes are attracted, and not plasma cells. He argues, therefore, that the interstitial exudate is primary and accompanied by, but not dependent upon, epithelial destruction.

With this battle of opposing ideas still pending, a further complication arose in a gradual change in the meaning of the terms parenchymatous and interstitial inflammations. This is perhaps best illustrated in Orth's position on the subject.

Orth[55] recognizes primarily a parenchymatous and interstitial nephritis, by which he means, however, *predominating changes* in parenchymatous and interstitial tissue respectively. *He uses these terms, therefore, purely in a descriptive sense, and not in any*

pathogenetic meaning. In this idea the largest number of pathologists and clinicians at present concur.

As a subdivision and intermediary form he regards glomerulonephritis. He states:[56] "It has been attempted from various sources to establish a uniform view for all the nonpurulent nephrites, inasmuch as some hold that the parenchyma cells are always primarily involved, others that all commence with a glomerulonephritis. I cannot agree with one or the other opinion; in fact, with no exclusive view at all. As far as I can see, a uniformity exists only in so far as any inflammatory irritant changes vessels as well as tissues, but I hold it justifiable to speak of various forms of kidney inflammation, because the different constituents of the kidney are concerned in a most unequal manner. Following, therefore, the principle 'a potiori fit denominatio,' I go so far as to acknowledge a parenchymatous, interstitial, and glomerulonephritis. But it must be remembered that no sharp line of demarcation between them is possible, and that their combinations are frequent findings." In this sense he describes a productive parenchymatous and a productive interstitial nephritis, of acute and chronic variety.

The ideas of Senator[57] have apparently been most widely adopted by clinicians. He holds that the differences in the forms of nephritis depend upon the course and the duration of the disease, and they, in turn, upon the intensity of the irritant. The stronger the latter, the more diffuse and extensive the involvement. The weaker irritant finds expression only in parenchymatous attack (tubules and glomeruli), while the interstitial tissue shows only hyperæmia. An acute interstitial nephritis without parenchymatous change is denied by Senator.

He, therefore, differentiates between an acute parenchymatous (in the sense of Orth) and diffuse nephritis. Strictly speaking, a chronic parenchymatous nephritis cannot exist, inasmuch as

after a time the interstitial tissue becomes always involved; but Senator holds that term admissible, to signify that these changes are primary and most prominent. But he disagrees, as pointed out before, with Weigert as to whether parenchymatous degeneration must always precede the interstitial change. He holds, moreover, that chronic inflammations of the connective tissue are rapidly followed by degeneration on part of the parenchyma, leading to induration. Chronic forms of nephritis result either from a previous acute condition or may develop independently. Chronic nephritis may also result from arterial changes in the kidney, leading to atrophy of glomeruli and tubules. Finally, any of these chronic types may at any time undergo acute exacerbations, producing new, very variable, anatomical and clinical pictures.

At a recent discussion of the German Pathological Society, Müller[58] again has revived the discussion about the impossibility, even clinically, of differentiating between acute and chronic nephritis, and the erroneous conception implied in speaking of parenchymatous nephritis, because the lesion is always diffuse and the interstitial tissue as much involved in the process as the parenchyma, even showing degenerative changes in the form of fatty infiltration (Löhlein). Again, in the so-called interstitial forms, it would be erroneous to believe that the parenchyma was not much involved and disintegrated, for glomeruli, as well as tubules, show severe changes. He further drew attention to the difficulty of any satisfactory etiological classification; and grouped off, much as formerly was done, degenerations from true inflammation of the kidney, and recommends grouping them as nephroses, as contrasted with nephritis.

Finally, we must regard the ideas of Löhlein,[59] which, coming from Marchand's Institute, represent mainly the ideas taught there. He also believes that in many cases, which involve almost

exclusively the renal parenchyma, as in the lesions produced by cholera, synanche, poisonings, pregnancy, etc., there exists no real inflammation, but a degeneration, which has a great tendency to heal, and probably almost always heals completely. The true nephritis is inflammatory and has its prototype in the glomerulonephritis. The parenchymatous changes there depend mainly upon the glomerular ones in their intensity and duration. Acute interstitial nephritis must, however, be considered independent. Chronic nephritis with hydrops results from all cases of glomerular nephritis which do not heal, or may commence insidiously without acute manifestation; in reality they represent the results of an acute nephritis.

Lastly, the secondary contracted kidney always presents anatomical evidences of a glomerular nephritis, which may be traced to previous acute lesions. It is certainly more frequent than supposed. In some of these cases the features are so characteristic that, without knowledge of the previous history of the individual, the diagnosis of nephritis can be made.

In this connection Löhlein emphasizes a type of case which, having passed through an attack of acute nephritis with hydrops, enjoys relative health for some time, then suddenly dies with all the symptoms of nephritis. Here is frequently found a typical chronic glomerulonephritis with severe contraction of the organ.

This, gentlemen, is an outline which, although incomplete and neglecting much and the works of many, seems to me to contain the salient disputed points. What may we conclude?

With regard to the question as to what to include under the general heading of Bright's disease, I think it has gradually developed to limit its application to the non-specific, hæmatogenous, non-purulent inflammations of the kidney, and we may exclude from it, therefore, all non-inflammatory affections, particularly the chronically congested kidney and its after-results,

further amyloid and fatty infiltrations, and, as will appear later, the senile atrophy of the kidney. Specific inflammatory lesions of known etiology or morphology have also, by virtue of their characteristic etiology and morphology, been eliminated, as well as ascending inflammations from the bladder.

I say that this opinion is gradually getting the upper hand; some seem to think that parenchymatous degenerative lesions should enjoy an independent recognition among inflammatory changes. To these investigators the term Bright's disease appears still indispensable as a more general one than nephritis. I cannot agree to that, for, whatever theoretical considerations may form the foundation of that idea,—and I consider them very slight indeed,—practically we not only gain nothing by this fine line of demarcation, but it forms the source of endless confusion. I shall qualify my position in this matter more fully later.

The term nephritis will therefore be used in the following discussions as synonymous with and instead of Bright's disease, because it has a certain definite meaning and cannot be misunderstood. We cannot agree as easily, and will probably meet much greater opposition, in defining our position on the second and most important point; namely, What are the characteristic features of this inflammation? and, subsequently, how the various inflammatory processes in the kidney may be adequately classified.

Here you must well remember what we reviewed a short while ago. The terms parenchymatous, interstitial, diffuse, persist like threads, but of ever-changing colors throughout the historic development of inflammation in general, and nephritis in particular. I hold that the sooner we break with their use, the better for the progress of knowledge, but particularly for our understanding of inflammatory phenonema and that of nephritis.

We have seen how the views of Virchow, Beer, Cohnheim,

Weigert, and others, after whom the words parenchymatous and interstitial inflammations were employed in a strictly pathogenetically contrasting sense, have not been upheld by future investigations. It is undeniable and clear that certain inflammatory irritants affect extensively and perhaps primarily the epithelium in degeneration and proliferation, and that there are others which similarly involve the interstitial and vascular system in exudation and production. Both are, however, always combined, correlated, and, at least after a short time, equally affected, so that in any established inflammation—in other words, in any nephritis—a differentiation between parenchymatous and interstitial inflammation becomes practically impossible. But with the pathogenetic meaning of these terms lost, their employment is no more justifiable, for I cannot even agree that these terms may be used in a purely descriptive sense.

Aside from the fact that it does not seem wise to me to continue terms in an arbitrary other sense, which is bound to produce return to confusion instead of an advance to greater clearness, this nomenclature has not even exactness in its favor.

We have learned, you remember, that many changes which some have predominantly related to the parenchyma, are equally well and severely represented in the interstitial tissue (fatty degeneration and inflammatory œdema). Again, in the so-called typically interstitial lesions, glomeruli and epithelium of the tubules are extensively affected and destroyed. Who could state, therefore, which were more affected in one case than in the other? Such an opinion can be based only on very superficial examination of diseased kidneys.

Equally objectionable, finally, are the two terms acute and chronic, for they not only do not describe with any degree of precision the time limit of a nephritis, or the rapidity of its formation and its progress, but they have lost in the course of patho-

logical investigations any definite significance with regard to a particular process or group of processes.

As Müller has pointed out, therefore, the terms acute and chronic have even lost much of their *clinical* meaning. When does an acute nephritis become chronic? Here is too much room for individual opinion and discussion. Moreover, kidneys are found at autopsy after short illness, showing lesions of a character now grouped as typically chronic; and, again, after long-continued illness, showing predominating changes of so-called acute character.

Nothing at all is, therefore, gained for the understanding of the pathological process by the terms acute, subacute, and chronic; they may even actually mislead.

For all these reasons, and to further progress in our knowledge of the inflammatory lesions of the kidney, I propose to discard all these terms, which, on account of the many ways in which they may be intended to apply, have and always will be the greatest source of confusion and a drawback to a better understanding of pathological conditions.

1. The term nephritis, which in itself means inflammation of the kidney, and which therefore comprises all the processes which are held to be component parts of an inflammation, should have added to it, when necessary, descriptive terms, not defining particularly the location of the inflammation or its pathogenesis, but purely descriptive of the predominating pathological feature or features. In this regard the classification of Delafield[60] was a considerable forward step.

2. In certain forms of nephritis, when predominating features are lacking or of minor importance, no such descriptive terms are required. These I group as nephritis simplex. This type is represented mainly by varying combinations of parenchymatous degenerations and inflammatory œdema.

3. When certain inflammatory attributes predominate, they are added as qualifications to the term nephritis. In this sense I speak of nephritis degenerativa, exudativa, hæmorrhagica, and prolifera. It may be one or more that are marked in this way. To signify any particularly prominent location, one can add tubularis or glomerularis.

4. When in certain kidneys fatty changes occur which assume great prominence, the lesion is spoken of as nephritis degenerativa adiposa.

5. When, in such kidneys, loss of parenchyma occurs with connective-tissue growth and vascular changes, the term nephritis degenerativa et productiva is employed.

6. When the loss of kidney substance is extreme, with a thick, fibrous, connective-tissue growth, marked vascular changes, and the degenerative changes not prominent, we may speak of nephritis productiva.*

7. Finally, there exists an atrophy of parenchyma, either alone or with marked arteriosclerosis and patchy fibrous-tissue growth, typified in the senile kidney, and, as I believe, really not of an inflammatory character. This is termed atrophia and sclerosis renum respectively. I include it here for the sake of discussion.

No doubt combinations of these forms and types, which we can recognize only in a wider sense, are frequent, and should then be named and classified accordingly. This point will appear more fully in a detailed discussion later.

I trust you have followed me sufficiently to appreciate the desirability of a break with the older, current classifications, and to substitute a simple descriptive terminology. I believe fully that only on the basis of clearer anatomical pictures, which this

* The term productive may seem objectionable to some, as the formation of new tissue concerns largely the supporting structure, but it is perhaps admissible when it is considered that far-reaching modification of cells occurs in the essential parenchyma.

nomenclature aims at, will better knowledge of the diseases of the kidney be made possible, not only for the minds of the investigators, who largely do not understand each other now and battle with words, but particularly for those diagnosing and treating them.

SECOND LECTURE*

The Structure of the Normal Kidney and the Different Views on its Functions in their Relation to the Pathological Variations

Gentlemen:

Before we enter upon our subject, I think it wise to recall to your mind certain histological and physiological facts and theories. Unfortunately, they are not as complete as we would like to have; particularly on the physiological side testimony is scant. The rôle played in the secretion of the urine by the various component parts of the kidney is not definitely settled; and if this knowledge is deficient on the physiological side, we are in a perfect chaos of conflicting testimony on the pathological side, into which we can bring light and reason only with much difficulty. We may admit from the start that there is really not one theory of urinary secretion which directly conforms with all the pathological evidence, and allows us to form clear conceptions of the pathological variations. The reason for this will appear later. Let us examine what evidence there is.[1]

Commencing with histological considerations, I believe I may disregard in these lectures the embryology, and immediately invite your attention, with the aid of this diagram, to the structures of the normal adult kidney (Plate 1). You know that it is composed of two easily recognizable and separable parts: The outer, or cortex, and the inner, or medulla, which stands in direct communication with the pelvis. Both of these enter, however, upon the field of the other, for, as you see, the medulla,

* Delivered on January 21, 1909.

by characteristic radiating lines, sends offsprings into the cortex, known as medullary rays; while masses of cortex separate parts of the medulla, the pyramids, by the so-called columns of Bertini. The medullary rays are produced by a regular interchange of vessels with the collecting and straight tubules, the ascending and descending loops of Henle. The cortex proper, on the other hand, contains the glomeruli and the proximal and distal ends of the convoluted tubules. Referring to the diagram, you appreciate the long and partly tortuous course of one of these units, commencing with the cortical glomerulus, and, after a long, varied route, ending in the pelvis of the kidney. Particular attention should be paid to the different caliber of the tubules in different parts, and the very abrupt change from the broad, convoluted tubule to that of the straight, narrow limb of Henle, with the interpolation of a second, but much shorter, convoluted portion, which finally empties into the collecting tubules.

I think it proper to briefly describe the main features of the blood-supply before speaking of their finer structure.

It is very suggestive. All conditions are given whereby a large amount of blood, under a very high pressure, can be brought to the kidney directly, without passing through many diverting channels. The renal artery is a rather short, thick branch, given off directly from the aorta. It proceeds to the hilus of the kidney, where it immediately divides into several branches which ascend to the point of junction between the cortex and the medulla. The first branch of the renal artery is spoken of as the interlobar artery, while its branches, which you see represented, are spoken of as the interlobular arteries. They proceed up through the cortex and down through the medulla. In the cortex they pass directly to the glomerulus.

The formation of a glomerulus is interesting. It is a lobular structure, composed of a vascular network, known as capillary

tuft, and enclosed in what is termed Bowman's capsule. It is, moreover, peculiar and characteristic that the afferent vessel of the glomerulus is very much larger than the efferent or centrifugal vessel. In other words, the blood is brought under high, almost direct, aortic pressure to the glomerulus, but in the glomerulus it is under still higher pressure and distributed over a relatively large surface. So much is plain from anatomical observation.

Having left the glomerulus, the vas efferens immediately breaks up into a capillary network, and this network follows the convoluted tubules. Before the blood reaches the convoluted tubules at all, it must go through a glomerulus, and the blood which goes to the tubules is under a relatively lower pressure, compared with what prevails in the glomerulus and, as will appear later, must have a greater concentration. The veins which correspond to these arteries are essentially the same, with the only exception that they do not enter the glomerulus.

The lymphatic vessels of the kidney are not very well known. It is supposed that they accompany the vessels. It is doubtful if there are any in the glomerulus.

With regard to nerves, there exists a complex derived from the renal plexus and lesser splanchnic. They accompany the vessels and also extend to glomeruli and, as some suppose, to the epithelium of the convoluted tubules. This latter point is uncertain, and the presence of secretory nerves has never been conclusively demonstrated. Nervous influence may be explained on the basis of vasomotor action.

We come now to the important consideration of the structures of the essential parts of the kidney. The glomeruli and the tubules are lined throughout by epithelium, but it is different epithelium in different parts. In the glomerulus, it is made up

of two layers. Epithelium lines the capsule and is reflected over the tuft, but only so as to partly cover this. It is stated by Herring[2] that the epithelium of the capsule is of a lower, more endothelial, syncytial type, while the reflected epithelium of the tuft is of a greater differentiation, and resembles somewhat the secretory epithelium. At the point of entrance of the first convoluted tubule the epithelium changes gradually, so that transition cannot be definitely established at any particular point.

The epithelium of the convoluted tubules is high, well differentiated. The nucleus is situated near the tunica propria. The protoplasm is extremely granular. These granulations are arranged in definite order of streaks or rods. Their extremities are delicately brushed with non-motile cilia.

The epithelium of the descending limb of Henle is low and flat. It is rather poorly defined, so that the line of demarcation between the different cells is not clear, and it looks more like a syncytial formation or the epithelium of the capsule of the glomerulus.

The epithelium of the ascending limb of Henle, as well as of the distal end of the convoluted tubules, is higher, and again becomes distinctly granular, somewhat resembling the epithelium found in the proximal limb of the convoluted tubules. This is given by some as cylindrical epithelium, a doubtful statement for the normal human kidney.

The epithelium of the collecting tubules, finally, is high, clear, and not granular, while the lumen of the tubule itself is very large. You can see, therefore, that there are essential differences in the make-up of these important structures. We are unable, however, to correlate with the same ease the functional differences. We have evidence which brings in a general way the epithelium of these various parts in relation to certain functions; but no

absolute proof exists as regards their specialized duties. Possible exceptions are only the glomerulus and the proximal convoluted tubule, about whose duties we are somewhat better informed than about the rest of the structure.

So much, then, for anatomical considerations. The arrangement differs from that of other glands mainly in the blood-supply and in the peculiar course and structure of the secreting surface.

I must now review the various conceptions which are held with regard to the secretion of urine.[3] The old idea had been that the kidney was essentially a filter, that is, a structure through which water and the characteristic urinary constituents were passed by a simple process of filtration. That idea gained ground particularly after Bowman's classical description of the glomerulus. But, on account of the length and the essential structural variations of the tubules, it soon appeared that a specific, secretory function on their parts was also probable. Thus Bowman (1842)[4] himself believed that the glomerulus filtered water, but that the tubes were a secretory structure, and he based his ideas entirely on the previously detailed anatomical considerations.

Ludwig, who in 1844 published his classical observations, at the time of strongest conflict between vitalists and mechanists, was the first to offer a purely physical theory.[5] In substance, this theory assumes that *all* urinary constituents transude through the glomerulus, under the force of its high pressure and in very dilute solution. Passing through the tubules a resorption of this water to the more concentrated lymph occurs; the fluid, therefore, assumes its urinous character.

Ludwig based his ideas of filtration on the fact that the amount of urine depends mainly on the arterial pressure and on the rapidity of flow in the kidneys. If the arterial pressure is

increased, and if the rate of flow of the blood through the kidney is also increased, then, of course, the amount of urine increases. If, on the other hand, we have a diminution of the arterial pressure in the kidney, and a diminution of the rate of flow of the blood through the kidney, then the amount of urine decreases. This is a perfectly obvious fact, and is also supported by pathological evidences. We know that in cases of incomplete compensation of the heart the amount of urine diminishes markedly. It is also certain that when the renal artery is obliterated, the same holds true; and when the arterial pressure in the kidney is markedly diminished, as in section of the spinal cord, there is a considerable diminution in the volume of urine. On the other hand, division of the renal nerves produces vasomotor paralysis on that side and the urine is increased. Stimulation of the spinal cord and the splanchnics raises the blood-pressure, and has, therefore, the same result.

Further corroboration is found in the close relation of the amount of fluid taken to that excreted, so that the quantity of urine depends largely upon the proportion of water present in the blood. If a person drinks large amounts, there is an almost immediate response on the part of the kidneys. The effects of certain drugs, like caffein and diuretin, have also been looked upon as favorable to this idea, inasmuch as their action is considered to depend upon an increase of blood-current due to a vascular dilatation, although this has been disputed.

Now, in order to explain certain properties of urine, which cannot be accounted for by the direct application of simple filtration, Ludwig resorted to another theoretical consideration, which, in his opinion, explains the complicated and perplexing structure of the tubules. He held that, while a transudation occurs in the glomeruli, resorption of water occurs in the down-

ward flow. This accounts for the relative concentration of the urine, which is much greater than that of the blood. In his opinion, therefore, the tubules exist mainly for the process of water resorption.

It must be confessed at once that there is no absolutely conclusive proof of water resorption by the tubules. The experiments of Ribbert on the increased flow of urine water after the resection of the medulla have been contradicted by Boyd, but later evidence along this line has been particularly offered and upheld by Cushny and Hans Meyer.[6] However, there is also much against it.

For, inasmuch as the urine has a higher osmotic pressure than the blood, it follows that a simple resorption seems to be out of question, but we must assume for this active work on part of the epithelial cells of the tubules. It has been figured out by Dreser[7] that, in order to effect this concentration, it would require, under circumstances, a force six times greater than that of human muscle (8000 gm. per square centimeter). (He deprived a cat of water for three days, and then drew off the urine, which had a freezing-point of $\triangle$ = 4.72° C. The blood at the same time had $\triangle$ = 0.66° C. Now von t'Hoff has shown, if $\triangle$ is the depression of the freezing-point, and T the absolute freezing-point of the solvent (for H_2O 273° and w the latent heat of fusion of ice = 79 cal.), then the work A can be reckoned from this formula:

$$dA = \frac{\triangle . w}{T} \times dv.$$

Thus for 1 per cent. solution of cane-sugar ($\triangle$ = 0.055):

$$dA = \frac{0.055.79}{273} \times dv.$$

To reduce this result to gravitation units, we must multiply

by 424, and thus find that to separate the volume dv of pure water as ice from 1 per cent. cane-sugar solution, a force is necessary equal to the pressure of a column of water of $\frac{0.055 \times 79 \times 424}{273}$ meters in height. A depression of $\wedge = -1°$ corresponds, therefore, to an osmotic pressure of $\frac{79 \times 424}{273}$; that is to say, to 122.7 meters of water. We have, therefore, to multiply $\wedge$ by 122.7 in order to obtain the osmotic pressure in meters of water in any solution.

In the case of the cat just mentioned, these differences in the freezing-point denote an osmotic difference of 498 meters water, *i. e.*, a pressure of 49,800 gm. per square centimeter!

Dreser has endeavored to show the same with regard to the glomeruli, to demonstrate in them also active work on part of the lining epithelial cells.)

From our standpoint there are, as Müller[8] has only lately pointed out, some objections to accept the pure filtration idea of Ludwig. We all know that in chronic venous congestion the amount of urine is much diminished, while the secretion of nitrogenous material is kept up to nearly normal limits, except in extreme cases of oliguria. How can Ludwig then account for this? One would have to suppose an almost normal transudation from the glomeruli with an *increased* resorption from the tubules. That seems unreasonable from physiological and teleological considerations, for an injured kidney would be called upon to do more work, to the injury of the patient.

For similar reasons, Müller holds an explanation of the large amount of urine in diabetes insipidus difficult, and the same applies to the increase in urine in certain forms of pure productive (interstitial) nephritis, where evidence showed greater affection of the glomeruli and less involvement of the epithelium of the tubules.

I will point out later, however, that we must be very careful to directly apply pathological functions for the proof or disproof of physiological contentions, as we have frequently entirely different anatomical conditions and rearrangements of the parts. I believe Ludwig's theory particularly weak in its lack of cognizance of certain metabolic functions on the part of the kidney, besides the elimination of urine. We know that certain synthetic processes are actively carried on in the kidney. The formation of hippuric acid from glycocoll and benzoic acid is perhaps best known and studied; yet there are undoubtedly others, like the formation of the urinary chromogens, etc. There can be no question that the epithelium of the tubules—of course, we do not know which—must be actively concerned in this formation, and that these substances are, in all probability, discharged directly into the tubules. It certainly appears that, if at all, a resorption of water cannot be the sole duty of the tubules.

These ideas of Ludwig have, therefore, been actively and permanently opposed, primarily by Heidenhain and his followers. Heidenhain[9] took the extreme other view, attributing the whole process to an active secretion, and denying any filtration. His ideas were essentially based on three points: If one ties the renal vein, the intraglomerular pressure is increased. In spite of that, the urine is not increased, but diminished. If one ties the renal artery and then releases it, the flow of urine is not immediately reëstablished, but only after a considerable time. These phenomena, he argues, speak against a simple transudative character of urine water. But the fact to which most importance is attached is the result of experiments after the injection of indigo carmin. He found that, if indigo carmin was injected into the renal artery and the animal was killed after ten minutes, the indigo carmin was always precipitated in the epithelium of the convoluted tubules. It was never found anywhere else. From

that he concluded a specific selective activity on the part of that portion of the renal epithelium.

Now, all of these three arguments of Heidenhain have not stood the test of time undisputed.[10] The results of tying the renal vein and thus increasing the intra-glomerular pressure without increase of urine, may easily be attributed to venous stasis. A diminution in the amount of urine may there be due to purely mechanical causes, namely, pressure of the parts against another, a result of the venous engorgement.

Similarly, the second argument, tying the renal artery, without, on its release, obtaining an immediate flow of urine, appears of doubtful value, because, in a complicated structure like the kidney, it would take considerable time before normal pressure and rapidity of flow are reëstablished in the glomeruli.

Finally, the most important argument which he advanced, the results obtained from injection of indigo carmin, has been denied its value by many investigators who claim that, if the solution of indigo carmin is not of the exact concentration Heidenhain employed, and if the kidney is examined early after injection, this substance is also found in the glomeruli, so that in reality selective activity does not occur. It has further been pointed out that on its way a good deal of the pigment might undergo a reduction, whereby it would not be visible in other cells, and, finally, much of the indigo carmin in the epithelial cells of the convoluted tubules is nearer the lumen of the tubule, so that one might argue that it were on its way from the lumen to the blood, and not vice versâ. This, of course, would conform with Ludwig's views.[11]

You see that these ideas of Heidenhain, although accepted by many, stand on a very disputed experimental basis.

Grave pathological evidence has also been brought forward against the sweeping secretory ideas of Heidenhain by Senator.[12]

We know a number of kidney lesions associated with extensive, although slowly progressing, destruction of the epithelium. Accepting Heidenhain's views of a purely secretory function of the epithelium, one should reasonably expect a gradual diminution in the amount of urine in these lesions. But the facts speak differently.

Pathologists and clinicians have known for a long time that in certain types of productive nephritis, and in the amyloid kidney, the amount of urine, instead of being diminished, is actually markedly increased. The gradual loss of epithelium of glomeruli and tubules does not seem to have the slightest relation to the urine output. How, asks Senator, can this be regarded as the active product of the epithelium?

Senator, in conjunction with Munk, began, therefore, to investigate that point further.[13] They were aided by a discovery, made shortly before by Roy and others, namely, that it is possible to have kidneys functionate after they have been removed from the body. Taking advantage of this method, they transfused defibrinated blood through kidneys, and were able to observe closely the results of changing pressure and rapidity of flow brought about artificially in transfusion. They found the following facts: In active hyperæmia – in other words, when the pressure as well as the velocity of the flow is increased – the quantity of urine excreted increases. The quantity of nitrogen increases, while that of the sodium chlorid shows very little variation from the normal. That latter point is interesting and important to remember.

Then they did the opposite, diminishing the quantity and the pressure through the kidney, with these results, that the amount of urine decreased decidedly, that the amount of nitrogenous material also decreased decidedly, while the amount of sodium chlorid showed no difference from the normal. Incidentally, I

should mention that the amount of albumin which such an artificial urine always shows diminished with arterial hyperæmia, and increased with passive hyperæmia. Interesting is the excretion of sodium chlorid, which remained practically unaffected by active hyperæmia or stasis. It argues for an at least partly transudative character of the urine, for pressure and rapidity of a transuding fluid determine the quantity of a transudate, but not its amount of dissolved crystalline substances.

Based on these considerations, they concluded that the urine must be regarded partly as a transudation and partly as a secretion. The transudative part is furnished by the glomeruli, the arrangement of which is also very much in favor of its being a transuding membrane. This, however, has added to it on its way through the tubules a secretion of the epithelium, which is also in watery solution. The combined fluid is taken up by the collecting tubules and discharged into the pelvis of the kidney as urine.

These ideas also have undergone revision by other investigators. It has been urged that it really has not been demonstrated beyond doubt that the glomeruli filter only water and sodium chlorid, and as a contradictory fact is mentioned that in argyria the silver impregnates the loops of the glomerular tuft. It is, therefore, argued that these tufts are probably permeable for other, normal, urinary substances. Again, it has been claimed that, if the glomeruli truly filtered, sugar as well as albumin ought to be found in normal urine.[14]

All of these objections, however, carry very little weight. That a foreign substance like silver is arrested in the glomerular tuft, which, on account of its arrangement, seems to be particularly exposed to the accumulation of foreign material within its loops, cannot, in my opinion, carry much evidence as regards normal functions. The other two objections have lost much

ground since it has become generally known that varying traces of albumin occur in all urines, and that sugar circulates in colloid form. Hans Meyer believes, therefore, that the glomeruli filter all the substances which are contained in the blood in crystalline form, while the convoluted tubules secrete such substances as are in colloid state (urea, uric acid, phosphoric acid). He and other investigators have revived for this latter process Ludwig's idea of water and NaCl resorption.

Hans Meyer, Cushny, and Hausmann found, as previously mentioned,[15] after extirpation of the medulla, an increase of from three to four times in urine quantity with a proportionate decrease in concentration. Meyer states that "the excretion of Cl and N after such operation corresponded to the contents of the blood, so that the fluid equaled an albumin-free blood filtrate."

Hans Meyer, Löwi,[16] Gottlieb, Magnus,[17] and Cushny also found that after injection of sodium sulphate (Glaubersalz) into the blood, a much more active diuresis occurred than after injection of a corresponding amount of sodium chlorid. Meyer concluded, therefore, that this acted similarly in the kidney as in the gut, prevented resorption, and caused, so to speak, a renal diarrhea. It has also been shown by Cushny, Pfaundler,[18] and Steyrer[19] that resistance in the ureters is associated with the secretion of a very thin urine. But this latter might easily be attributed, as Erich Meyer[20] remarks, to a kidney injury which interferes with its secretion.

Against the idea of filtration of dissolved crystalline substances by glomeruli and secretion of colloid compounds by the tubular cells, again are Asher and his pupils,[21] who found no regularity in the excretion of urine water and NaCl, and conclude, therefore, secretion of even these substances.

Asher furthermore points out that even specific glands, like the salivary, show a proportionate relation of dissolved blood

constituents and water. But it must be remembered that no other pure gland responds so instantly to changes in the concentration of the blood.

Finally, Erich Meyer,[22] who has studied very carefully the elimination of urine in diabetes insipidus and other polyurias, is of opinion that this urine cannot be regarded as a filtrate of blood-serum, inasmuch as it is too dilute as regards its total concentration, but as regards urea, about ten times as concentrated. For instance, in a case with a total urine amount of 8000 c.c. and a nitrogen excretion of 11 gm. pro die, the percentage of urea contents would be about 0.3, while, according to Gottlieb, the blood only has a concentration of 0.03 to 0.05. On the other hand, the Cl content of this urine was on some days almost ten times less than that of the blood. He further found that the diuretic theocin, produced in diabetes insipidus an increase of concentration without increase in quantity, but this could not be explained by a disturbance of resorption.

Similar to the modernized conception of Ludwig are the ideas of Koranyi,[23] whose views I will mention in detail, because they acquired considerable practical importance.

He believes that the glomeruli filter only water and sodium chlorid, but that in the tubules occurs an equimolecular exchange with metabolic products: a purely physical process. The sodium chlorid of the urine is, therefore, inversely proportional to the amount of nitrogen. Based upon this fact, which is actually found in a number of conditions, he established the so-called urinary quotient. This is obtained by dividing the freezing-point Δ of the urine by the amount of sodium chlorid, $\frac{\Delta}{NaCl}$ = urinary quotient. This quotient, in Koranyi's opinion, depends upon the rapidity of flow of blood through the kidneys: With diminished flow the quotient is high; vice versâ, with increased

flow the quotient is low. This has been found correct in cases of heart disease with failure of compensation and œdema.

It is interesting to know that in cases of orthostatic or physiological albuminuria the quotient has been found high, very much as in circulatory disturbances, while in true nephritis with albuminuria it was about normal, provided no change in heart compensation occurred. It has, therefore, been urged to employ this method for differentiation of orthostatic and nephritic albuminuria. Here, again, repeated investigations have been unable to maintain what was originally claimed. Müller, for instance, states that it fails, particularly, in the convalescence of pneumonia, as well as in diabetes insipidus, when the percentage of chlorids and achlorids rises and falls synchronously.

One fault of these theories, as in the old conceptions of Ludwig's, is their disregard of the metabolic activity of the kidney, besides elimination of preformed nitrogenous waste-products from the blood. This must certainly be carried on by the tubular epithelium, and the products discharged by them into the tubules. Moreover, analysis of anatomical and physiological evidence indicates that the production of urine can not be regarded as one uniform process. This complexity undoubtedly accounts for the many in parts conflicting observations and opinions.

In the production of urine there appear to be concerned two processes: The first is transudation, and the second secretion. The structure of the glomerulus, as well as what we know of its function, supports the contention that we have here a process of transudation. (Recently Brodie has further emphasized the fact that the glomerulus acts a good deal like a pump; by virtue of the elastic capsular fibers the filtered water may be put under high pressure, in which it is aided, of course, by the abrupt narrowing of the tube below. Thus it flushes away the secretion of the epithelial cells.) That the glomerular epithelium is secre-

tory seems improbable, for the reason that it only partly covers the glomerulus, that it has not the morphotic character of secretory cells, and that, under pathological conditions, water discharge continues after its loss, unless there is a mechanical obstruction to its outflow, or the tuft becomes diseased. This is particularly well illustrated in cases of contracted kidney, and in some cases of stasis, when the epithelium has been lost, but the tuft itself remains and still functionates. It is further corroborated by the fact that the reaction of the glomerular product has been found alkaline, and that on increased diuresis the urine becomes alkaline, and lastly by the constant presence of varying faint traces of serum albumin in all urines. The glomerulus, therefore, is that organ whose duty it is to regulate the concentration of the blood.

Now, we must remember that this water, which is furnished by the process of transudation from the glomerulus, is modified on its way. That modification cannot, I believe, be explained, at least at present, on a physical basis. We must assume that the epithelium of the convoluted tubules, as well as that of the other tubules, plays an active part in the modification of that fluid to urine. The reasons for it are these: The osmotic pressure of the urine is much higher than that of the blood, and it contains specific substances, and in such varying amounts, that an active part of these epithelial glandular cells is made most probable. It is undoubtedly for this reason that the blood is furnished to the epithelial cells of the tubules in a much more concentrated form. The change from alkaline blood plasma to acid urine, however, can be explained on physical basis.

The anatomical arrangement of the tubules indicates that there must be stagnation of the transuded water in the convoluted tubules. This may be for the sake of water resorption, but to me it is rather more for the purpose of complete solution of nitrogenous elements discharged by the epithelium of these

tubules. This is in harmony with the observations made in cyanosis of the kidney, where the urine water is diminished, but the nitrogenous contents about normal. On account of the venous stasis, less water transudes through the glomeruli, but the functions of the epithelial cells are carried on properly, until they begin to suffer from nutritive disturbances. The urine is, therefore, concentrated. A theory of exclusive water resorption would hardly account for this phenomenon.

It is also possible that water resorption occurs only when the amount of transuded water exceeds certain limits. We must confess ignorance of the specialized functions of the various parts, and types of epithelial cells, composing the tubules, and of the details of the secretory act.

A few words about the discharge of the urine from the pelvis of the kidney into the ureter and bladder. The physiological text-books leave us in the dark about the mechanism of this process, although we are informed that the urine is propelled by active contraction of the ureters into the bladder, and that a return flow from the pelvis into the tubules is made impossible by compression of the tubular orifices by any increase in pelvic pressure. Both pelvis of kidney and ureter have essentially the same structure; they are strong, elastic, muscular organs, lined by mucous membrane, and it appears probable that the active waves propelling the urine through the ureter into the bladder take their origin in the pelvis and similarly force the urine into the ureter. This has for us considerable interest. In many long-continued diseases, but notably in the senile kidney, there occurs marked weakening of the elastic muscular layer of the pelvis, with the result that this gradually dilates to a condition of hydronephrosis, although no mechanical obstruction outside of the kidney exists, and the ureters and bladder are not dilated. In these cases the pelvis evidently loses its power of active discharge into the ureter.

I believe that this covers as much as we are justified to assume at present about the secretion of urine. Much is still uncertain and contradictory. We confess its deficiency and uncertainty, and there exists great difficulty in the application of the experimental physiological knowledge for the explanation of diseased functions. In this connection, I would like, however, to emphasize certain points, which may, at least to some degree, account for these discrepancies. It appears that we are unable to transpose directly physiological knowledge for the explanation of pathological phenomena for the following reasons: The pathological organ is essentially a different organ from the normal. It presents more than simple alterations of physiological processes, in exaggeration, diminution, or abolition of certain functions which depend on similar organic changes. It is really incomparable to the normal organ from which it developed. Its whole architectural arrangement is changed by the formation of new tissue and the introduction of new cellular elements; its channels of nutrition, lymph, and nerve distribution become fundamentally altered; secretory ducts are lost; new ones are created; new cell types develop from the preëxisting parenchyma cells; in short, the pathological organ is a new one, characterized by tissue of its own and specific arrangement of its parts. No wonder, therefore, that it presents functional phenomena, which cannot be fully covered or explained by a direct application of the results of simple physiological experimentation and consideration derived from the normal organ.

Here is a future field for pathological anatomy. It can no longer be satisfied to describe and disclose *tissue changes*, but it must construe the plan of the whole *pathological organ*. Only a knowledge of both will ultimately lead to an intelligent understanding of pathological functions of a whole organ, and establish a pathological physiology commensurate with the normal.

THIRD LECTURE*

The Degenerative and Exudative Features of Nephritis

Gentlemen:

Following the classification indicated at the end of the first lecture, I turn to a detailed description of nephritis simplex. I understand by it a diffuse inflammation of the kidney, characterized by parenchymatous degeneration and inflammatory œdema; that is, serous exudate with diminished resorptive ability. This type of kidney lesion is now variously classified as acute nephritis, or acute parenchymatous nephritis, or acute parenchymatous degeneration of the kidney. The impropriety of the first two terms I have already covered, but I am obliged to pay some attention here to the last,—the acute parenchymatous degeneration of the kidney,—inasmuch as strong attempts have been made, only quite recently again, to separate the degenerative lesions of the kidney from the inflammations. This has been strongly advocated by Müller,[1] who wants to substitute the term nephroses for all such non-inflammatory but essential degenerations, and Marchand, and Löhlein and Heineke,[2] with some others, look more or less favorably upon such classification. The evidence for it is that there exist some diseases, cholera foremost, and some intoxications, like those of phosphorus, chromium, and corrosive sublimate, in which extensive parenchymatous degeneration occurs primarily and prominently, which may or may not become associated later with inflammatory hemorrhages and cellular exudate, and finally with productive interstitial changes.

* Delivered on February 4, 1909.

Marchand,[3] speaking of the kidney changes in corrosive sublimate poisoning, argues that one is not justified in regarding the initial lesion as a nephritis, inasmuch as the degeneration is the direct primary effect of the poison, and that death or regeneration may occur without additional inflammatory reactions. These latter, he holds, are only the late result of a chemotactic action caused by the accumulation of necrotic cell material and not reduced by the poison itself, which has long before ceased to exert its influence.

But Marchand himself admits—and this is very evident to any one reading the descriptions of Heineke's cases of corrosive sublimate kidneys that the lesion is associated from the start with considerable serous œdema; he attributes this, however, to a non-inflammatory, increased capillary permeability, and possible lessened resorption, analogous to the amyloid kidney, and bases this view on the absence of hyperæmia and hemorrhages.

It is difficult to follow this attempt of a finer classification in either substance or form. In reading over the careful work of Heineke on the subject, it appears that the lesion presents itself primarily as a marked parenchymatous degeneration with inflammatory œdema, followed soon by a cellular exudate and later by productive interstitial changes. To sharply separate the primary parenchymatous degeneration from the accompanying œdema, and again the almost immediately following cellular exudate, seems to me somewhat forced, and based on theoretical considerations, which are open to some criticism. Who, for instance, in the inflammations of the lung, would regard the initial œdema which precedes the cellular exudate as non-inflammatory, and genetically unrelated to it?

The absence of general hyperæmia and hemorrhages cannot be taken as proof against the inflammatory character of the

lesion, inasmuch as any inflamed organ with much swelling and inflammatory œdema of its parts, is generally anæmic. Furthermore, it appears from Heineke's description that in early cases "the cortical capillaries, the glomerular tufts, and the medullary capillaries showed frequent abundant blood injection." (See particularly his Case 1 of seven hours: "The glomeruli dark red, equally the peripheral portions of the pyramids."[4]) I can interpret this only as an inflammatory hyperæmia. This, of course, becomes lessened and more irregular as swelling and inflammatory œdema progress. Further, it is no à priori certainty that the appearance of the cellular exudate depends only upon chemotactic action of necrotic cellular masses. Other factors may enter into this, the discussion of which, however, would lead us too far from our topic.

I feel unconvinced, therefore, that we are justified in establishing an independent category of nephroses or parenchymatous degenerations independent of inflammations, as Müller would have it. Indeed, even Marchand is quite conscious of the additional difficulty thus introduced, for it would still become necessary to again apply qualifying adjectives. How much, for instance, would be gained by speaking of parenchymatous or degenerative nephrosis or of an inflammatory nephrosis? The latter, particularly, would soon lead back to a confusion from which we are only too anxious to escape.

We will therefore not recognize in our study a non-inflammatory, parenchymatous degeneration.

Now, to return to the discussion of simple nephritis: It is the form which is most frequently found in connection with all types of fevers, such as typhoid fever, the early stages of scarlet fever, synanche infections, cholera, septicæmia, and others. It also occurs in toxic and cachectic states and in some poisonings.

Such a kidney, grossly, varies little, if any, from the normal

in size, but appears swollen. The capsule is stretched thin, but can be stripped off with ease. The surface bulges, and this can frequently be seen under the thin capsule; it is smooth, and has usually a sort of dusky-gray, pinkish color.

That, however, is open to some variations: Occasionally, the surface may show distinct areas of vascular injection, but on account of the pressure of the swollen and œdematous parenchyma, the superficial veins are usually not at all prominent, and sometimes cannot be made out at all. Again, they may appear more prominent in places, and lost in others, on account of unequal distribution of inflammatory changes and consequent compensatory changes in the blood-stream. On section, the kidney shows conditions similar to those observed on gross examination. The cortex always bulges and appears relatively prominent. The markings show irregularities and the glomerular rows, instead of presenting a very definite arrangement, are distorted. The glomeruli appear in spots very prominent on account of a very marked vascular injection, and in others they may have disappeared altogether, or they can be recognized in the form of fine, grayish, slightly elevated points. They seem to be raised over the surface of the cortex. Such rows of glomeruli are separated by thick, gray, swollen, tubular masses. Occasionally, one can squeeze from the kidney a certain amount of œdematous fluid; this, however, depends entirely upon the amount of serous exudate. Where all of this has been imbibed by the structures of the kidney, it may even be dry and firm.

Similar conditions prevail in the medulla. The medulla, instead of appearing clear and definitely striated, is rather dull, grayish, swollen. The medullary rays are prominent, pale, and œdematous, while the interpolated vessels are for this reason obscured or, for compensatory reasons, appear in places much more prominent than they ordinarily do (Fig. 1). Pressing

Fig. 1.—Nephritis simplex, from general septicæmia following middle-ear disease. Cloudy swelling and serous exudate. Some of the glomerular rows with inflammatory engorgement, but generally the cortical markings lost or disturbed by cloudy swelling and serous exudation into the parts. Similar state in the medulla. Microscopically, this kidney showed no cellular or fibrinous exudation, but cloudy swelling of cells, swelling of glomerular endothelium and epithelium, and serous exudate into the glomerular capsule and interstitial tissue. Weight, 250 gms.

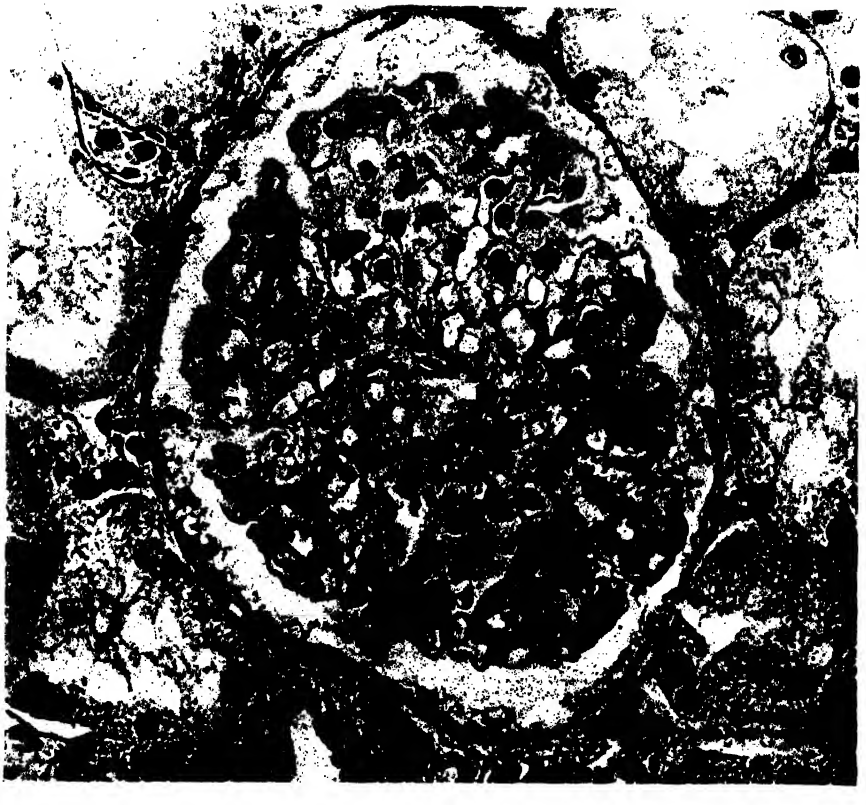


Fig. 2.—Nephritis simplex: Inflammatory engorgement of glomerular capillaries, with general enlargement of the tuft, cloudy swelling of its endothelium and epithelium; the latter partly desquamated. Granular disintegration of the capsular epithelium. Occasional engorgement of intertubular capillaries. Cloudy swelling and granular disintegration of tubular cells, with occasional nuclear degeneration.

gently on the medulla toward the pelvis, we are frequently able to discharge from the papillæ a slightly turbid fluid, and on examination that fluid is found to consist, to great extent, of desquamated tubular epithelium. This leads us to the microscopic appearances.

We observe, here, certain variations from the normal, which are more or less evenly distributed throughout the whole kidney substance. In the simplest and earliest forms, the more prominent features are turbidity of the glomerular tuft, serous exudation into the glomeruli, and a parenchymatous degeneration of the epithelium of the convoluted tubules. The glomerular capsule appears usually quite large, and, in the well-established cases, surrounded by œdematous tissue. The epithelium of Bowman's capsule is turbid, and so is the epithelium which is reflected over the glomerulus. In a certain number of glomeruli the capillary tuft is very markedly injected; in others, inflammatory swelling and turbidity of the capillary endothelium evident and soon followed by a serous exudate, so that the glomerular tufts appear thick and plump and fill the capsule. In this way glomeruli gradually lose their hyperæmic form. Then a serous exudate, demonstrable by its coagulating on hardening, can be seen in Bowman's capsule. If that exudate assumes any marked degree, the tuft is compressed by it, and thus its circulation necessarily much interfered with. If this process assumes any dimensions, the capsule becomes dilated, while the tuft itself is further pressed against one part of the capsule, usually at the entrance of the vessels; such glomeruli appear then as the fine, slightly elevated, pale, granular dots, noticeable on the cut surface of the cortex (Figs. 2 and 3).

In the majority of cases of simple nephritis that point is not reached, at least not in the majority of glomeruli, and they

remain turbid, swollen, and the capillary walls thick, pale, and plump.

The changes in the epithelial cells of the convoluted tubules are more evident at first sight than the changes found in the Malpighian corpuscles. They consist of varying degrees of parenchymatous degeneration (Fig. 4). The nature of parenchymatous degeneration is in itself a very important and fundamental study of general pathology. I take it that you are familiar with the essential features of it from your previous studies. But it may not be amiss if I shortly summarize once more for you the present knowledge regarding it.

The kidney from the time of Virchow[5] has been, above all others, the favored organ for investigations into the character of parenchymatous degeneration. Virchow, whose ideas on its nature I have already presented, introduced the appropriate descriptive term of "cloudy swelling"; and these two words express well its appearance. Such cells lose their definite normal structures and outline. The delicate, rod-like striation, composed of a regular arrangement of fine granules (Altmann's granules), which, as you remember, forms a feature of the protoplasm of the cells of the convoluted tubules, becomes disturbed, irregular, the granules more numerous, coarser, and more prominent; the cell as a whole appears darker. The finely brushed extremity may be lost. The cell enlarges, appears succulent, swollen, turbid, and plump, and occasionally as if dusted with granules. This has given rise to the term "granular degeneration." These granules are insoluble in chloroform, ether, and alcohol, but soluble in acetic acid and weak alkalis, and have therefore been regarded as of an albuminous character. There may be present, however, other larger, hyaline, globular bodies. They are regarded by some as the product of a pathological secretion. I shall say more about these in the discus-

Fig. 3.—Nephritis simplex: Glomerular capsule distended by serous exudate. The tuft compressed and adherent to part of the capsular wall, whose epithelium is relatively well preserved; cloudy swelling and œdema of surrounding structures. × 210.

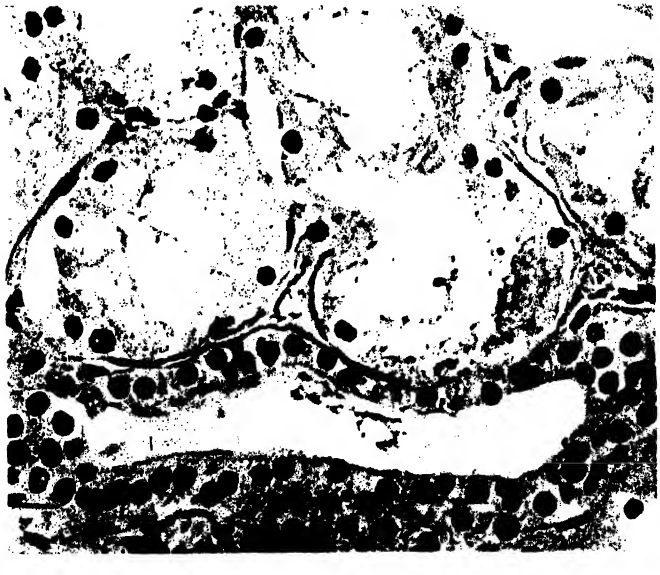


Fig. 4.—Granular disintegration of convoluted tubules. A better preserved loop of Henle.

sion of tube-casts. The nucleus is primarily unaffected, and is involved only in progressive and severe lesions. Its changes are those of chromatolysis, *i. e.*, a centrifugal loss of chromatic substance, and, as Benario[6] holds, are similar to those observed within the protoplasm. The outcome of this form of degeneration varies. In the simple nephritis, when the nucleus is not destroyed, restitution to integrity is probably the rule, *i. e.*, the majority of cells recover. Others, however, may go on to complete destruction, the cell membrane becomes lost, and the protoplasm disintegrates into a granular detritus and dissolves. When such severe changes are absent, but the parenchymatous destruction continues, the appearance of fatty substances becomes pronounced. I shall leave the discussion of this subject to a later date, when we are dealing with the fatty type of nephritis.

Opinions about the nature of parenchymatous degeneration differ widely. It involves two main questions: What is the derivation and significance of the granules, and what the origin and significance of the swelling of the affected cells?

Both were easily explained by Virchow's conception of overnutrition of the cells. Only shortly before his death Virchow declared: The swelling, as well as the cloudiness, depend upon a permanent assimilation of soluble substances, which are precipitated within the cell and undergo further changes. The swelling is, therefore, not caused by the usual nutritive, but by changed material.[7]

An entire change in these ideas went necessarily with those of the character of inflammation, for inasmuch as the parenchymatous degeneration was no longer considered a nutritive disturbance, but the direct result of an injury, it became necessary to explain the cloudy swelling in some other way.

It has, therefore, been variously considered either as a granular precipitation of normally dissolved proteid (Rind-

fleisch,[8] Cohnheim[9]), or as a coagulation (Klebs[10]), or, more generally, as a disorganization of protoplasm with resorption of fluid (Ziegler[11]), or as a regressive metamorphosis due to undernutrition (Thoma[12]). Some, like Birch-Hirschfeld[13] and von Recklinghausen,[14] retain partly the views of Virchow. The former believes that it represents an accumulation of undissolved or precipitated proteids as the result of increased proteid destruction with an increased supply of proteid; the latter regards it as an increased functional activity similar to the increased production of mucus in the catarrhal inflammations of mucous membranes.

Considerable experimental work on the subject has been done. Schilling[15] obtained cloudy swelling of one kidney forty-eight hours after tying the renal vein of the other. He concludes, therefore, that this must be the result of compensatory action on part of that kidney, caused by the increased amount of urinary constituents in the blood, a forerunner of hypertrophy. Landsteiner,[16] however, has pointed out that these results are not identical with those of infections or intoxications. The cells of the first convoluted tubules were left entirely free, and the lesion remained strictly localized to the cells of the proximal convoluted tubules. This is the very opposite from what is usually observed in disease.

Such experiments are entirely unconvincing for explanations of either hypertrophy or parenchymatous degeneration, for the reason that such an interference suddenly produces marked complications in the functions of the other kidney, and to such an extent that one is not justified in drawing any conclusions from it. One might interpret these results as moderate injury to a particular group of cells of the kidney, caused by the sudden changes in circulatory conditions and the increased amount of urine constituents. There is no evidence, as far as I

know, which could corroborate the view that parenchymatous degeneration bears a genetic relation to hypertrophy.

There is no uniformity of opinion about the derivation of the granules. While some look upon them as an increase of the normal type, Galeotti [17] holds that they represent a different aggregate condition of the cytoplasm, while the normal granules disappear. Based on Naegeli's theory of protoplasm, he holds that the proteid molecules lose their ability for the formation of micellæ, which are the fundamental requisite of life, and the new granules thus resulting represent the first evidences of cell necrosis.

It will be seen that views about parenchymatous degeneration are largely dependent upon the theoretical conceptions of protoplasm. This is, perhaps, best illustrated in the most recent ideas of Albrecht,[18] who regards protoplasm as an emulsion, which, under various influences, particularly water, loses its homogeneity, and changes to a mechanical mixture which contains drops of one substance suspended in the other (tropfige Entmischung).

Based on his own studies, Landsteiner [19] concludes that the process is essentially a destruction of the filamentous structure of the protoplasm with clumping into granules. The swelling is to be attributed to the destruction of the protoplasm. He is inclined to attribute the whole to autolytic processes. Similar are the views of Orgler and others, who, having found substances of the myelin group in such cells, look upon it merely as a myelinic degeneration, or, better, disorganization of the protoplasm —an autolysis. I shall say more about this later in connection with the fatty types of nephritis.

Adami [20] holds to the possibility of increased absorption of food-stuffs, with imperfect conversion and utilization of the same, and differentiates it distinctly from granular degeneration or the

"tropfige Entmischung" of Albrecht. This he regards as a disintegrative condition of the cytoplasm, an indication of cell death, and allied to the granular degeneration described by Verworn in injured infusorians.

From my own observations I believe that the process depends upon outside influences which, either by excessive stimulation of the cell activity, or by direct harmful influences, produce disturbances in the composition of the protoplasm which necessarily lead to changes in the organization of the parts, and temporary or permanent cell injury. The appearance of the granules I also regard as an indication of changed protoplasmic constitution, whereby the normal composition and arrangement are gradually lost; and I attribute the swelling to the thus altered physical conditions of the cell and *its changed environment.* Depending on the degree of injury and the correlated disturbances in the protoplasm, the cell either adapts itself to the new environment or changes its character entirely by undergoing further degenerative (fatty) changes or complete disorganization.

I have endeavored to recall to your mind these fundamental principles of general pathology because they play so important a rôle in the correct and clear conceptions of nephritis, and we will have to refer to them frequently in our subsequent study.

To return to the subject of simple nephritis, I shall only have to add that the tissue between the tubules shows the same inflammatory œdema which I have already mentioned in connection with the periglomerular tissue. It is stretched, hazy, separated by œdematous fluid. The intertubular capillaries are in parts engorged or may be compressed.

The result of simple nephritis is restitution to integrity in the majority of cases. The inflammatory œdema subsides and, after clearing of the lymphatics, is resorbed; the glomeruli and the vascular apparatus, not having undergone permanent injury,

assume their former condition. The epithelium also regenerates rapidly, inasmuch as only little of it has undergone actual necrosis, and the kidney may, therefore, be said to recover completely, unless conditions supervene which, prolonging the interference, gradually lead to the more severe types of kidney inflammations which I am now about to describe.

Before that, however, a few words about the functional changes in these cases of simple nephritis. The structural changes in the vascular apparatus, as well as the mechanical conditions in the swelling of the parts, result necessarily in a much diminished amount of urine, of relatively high concentration and specific gravity, high colored—the typical so-called fever urine. Serum-albumin is usually present, and, depending upon the amount of inflammatory œdema into glomeruli and tubules, never more than in traces. In morphotic elements this urine is poor, as the process never leads to extensive loss of cellular elements, and the exudate, as we saw, is purely serous. The first indication of recovery is rapid increase in the amount of urine, which indicates clearing of lymphatics and capillary engorgement; with return to physiological functions, albumin disappears and the urine loses its increase in concentration.

Closely allied to nephritis simplex is a type which is characterized not only by parenchymatous degeneration and inflammatory œdema, but by a marked desquamation of epithelium and excessive proliferation of the same. To this subdivision the term nephritis prolifera might properly be given as distinguishing it from the simple form. It was called by Virchow the catarrhal form of nephritis; later it was much neglected, but recognized by Orth [21] and Kaufman [22] as desquamative and proliferative papillary catarrh on account of its predominating appearance in the medulla of the kidney. In this form we may squeeze out, at autopsy, an abundance of turbid

fluid from the medulla, consisting of epithelial cells and detritus. It is, however, by no means confined to these tubules, but occurs diffuse, as recent investigations of others and my own have shown; it is seen particularly in cases when the parenchymatous degeneration of the epithelium is marked, and much of it destroyed and lost. It may, therefore, become associated with all other types of nephritis, and plays, as I presently hope to show, much more of a rôle in the inflammatory process than is usually supposed (Fig. 5). While Virchow had observed the desquamation of the epithelium, it was shown by Beer in 1859 that these cells rapidly and excessively proliferated, that the tubules dilate and are frequently filled with these cell masses.[23] He regarded this lesion as an inflammatory phenomenon.

Later observers, like Weigert,[24] Golgi,[25] and others,[26] studied these cell types more carefully and described the formation of epithelial giant-cells in nephritis (Fig. 6). But the idea gained ground that they represented either true regenerations, or, at least, regenerative attempts with failure. The studies of Arnold[27] and Baumgarten[28] on the formation of tubercles in the kidney connected this proliferation more definitely with the defenses of the tissue against the tuberculous invasion, and my own studies in the matter have convinced me[29] that we have here before us a type of parenchymatous inflammatory reaction analogous to the excessive epithelial proliferation in certain other inflammations; for instance, in the lungs, in catarrhal pneumonia. I was led to this view because of the predominance of an irregular cell activity and atypical cell forms, to which we cannot attribute any normal restitution or normal activity, the formation of syncytial giant-cells, and the excessive intracanalicular proliferation. The latest observations of Heineke[30] on the kidney changes in corrosive sublimate poisoning have brought corroboration of this contention, for he too observed the same

Fig. 5.—Nephritis prolifera et productiva: Parts of Henle's loops filled and dilated with newly formed cells, recognizable by their size, shape, protoplasm, and richly chromatic nuclei. One very large convoluted tubule filled with necrotic cell masses, a smaller one above. The intervening fibrous tissue thickened. × 360.

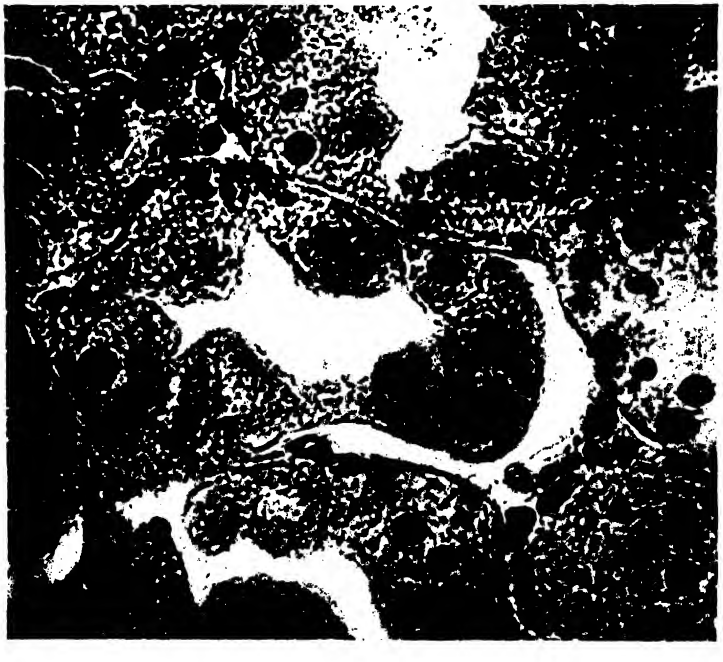


Fig. 6.—Formation of multinuclear giant-cell in a convoluted tubule.

diffuse, excessive epithelial proliferation. These cells, moreover, were distinctly phagocytic to the necrotic cell masses. In this way several generations of epithelial cells were produced, disintegrated, and eliminated before true permanent regeneration commenced. The epithelial proliferation in nephritis is, then, an inflammatory phenomenon, and should be appreciated as an important factor in the pathogenesis of the inflammation.

Functionally the lesion becomes evident by the free discharge of the newly formed and desquamating cell masses and epithelial detritus in the urine. This, therefore, is richer in morphotic elements. Microscopic examination shows these cells in a free state, when they are frequently mistaken for leukocytes, or in the form of cellular or granular casts.

This leads directly to the important and severe kidney inflammations, which I group under the category of nephritis degenerativa et exudativa. As the name and its adjectives imply, we include here types in which either the degenerative or the exudative features predominate, or in which both appear so intense and characteristic, and lead to such permanent alterations in the organ, that quantitatively and qualitatively they go far beyond the lesions of simple and proliferative nephritis.

It is in these complicated forms of nephritis particularly that opinions differ widely as to pathogenesis and histogenesis. I have already sketched in the introductory lecture the fundamental questions which are involved, but it is necessary here that some attention be paid at least to the more important details of the discussion.

You will remember from my first lecture, and from what I said in the beginning to-day, that modern pathologists are divided into several camps as regards the conception and definition of inflammation.

One group adheres to the old term of parenchymatous in-

flammation. Aschoff, for instance, in his new book on pathological anatomy, states: "As long as cloudy swelling of the tubular epithelium controls the picture of the inflammatory reaction without particular change in the vascular connective tissue and the glomerular bodies, one is justified to speak of a tubular nephritis." The parenchymatous degeneration is taken as the result of an inflammatory reaction and represents a condition of increased secretion with increased formation of protoplasmic granules, colloid and fluid drops, and vacuoles. Exudative processes are looked upon either as an accompaniment or result of the epithelial irritation.

This view has, as you see, a relation to the old, previously discussed ideas of Virchow on parenchymatous degeneration and inflammation. But it differs from them essentially in regarding the parenchymatous degeneration as an *active* process, the direct result of an injury which is followed, and not caused, as Virchow would have it, by exudation. Parenchymatous inflammation is, therefore, the prototype of an inflammation; only when the epithelium is killed the inflammation becomes modified.

A second group restricts the inflammatory conception solely to the vascular and exudative reactive changes, and divorces the degenerative features absolutely from them. These latter may, in the minds of some, either precede and excite the inflammatory changes (Marchand, *l. c.*), or they may initiate and cause a degenerative parenchymatous involvement.

Nauwerck[31] has come out particularly strong for the latter view in nephritis in an attempt to disprove Weigert's conceptions, but von Kahlden[32] properly remarks that in an extensive study he has never met such cases.

A third group, finally, holds, to quote with Lubarsch, that only the combination of, and intimate correlation of, alterative, exudative, and proliferative changes constitute inflammation.

This group of investigators eliminates entirely from the inflammatory conception the degenerative parenchymatous processes, and does not, therefore, tolerate the so-called parenchymatous inflammations of the older writers. It rejects, for instance, entirely the term of parenchymatous myocarditis, neuritis, myelitis, and so forth. It denies the inflammatory character to purely nutritive and alterative changes in the parenchyma, unless combined with exudative and proliferative changes.

It is this group of investigators which would separate, in the case of the kidney, as we saw in the beginning of this lecture, a non-inflammatory parenchymatous degeneration as an essential, but not a nephritic, lesion.

One can recognize, therefore, various attempts of classification on the part of investigators:

1. Degenerative changes in the parenchyma form the essential feature of nephritis; and they may or may not be accompanied or followed by vascular exudation.

2. Vascular exudation is the characteristic phenomenon of a nephritis: (*a*) This may or may not become associated with degenerative changes in the parenchyma. (*b*) It depends upon the parenchymatous destruction. (*c*) It may involve the whole vascular apparatus of the kidney or only parts of it (glomerulonephritis).

3. All established inflammatory affections of the kidney are diffuse; that is, they involve all the structures (parenchymatous and vascular) of the organ, although they may be unevenly distributed. An absolute dependence of one change upon the other cannot be made out, although at the beginning either degenerative or exudative features of the process may appear more prominent, and in a number of cases may continue so.

This latter standpoint appears to me the most acceptable one, with the following qualifications:

(*A*) The term inflammation comprises the sum total of those correlated but not absolutely dependent degenerative, proliferative, and exudative changes which are the direct result of an injury to a part. Pure degenerative and proliferative, as well as pure exudative, inflammations do not exist, although, for reasons to be discussed later, one of these inflammatory attributes may become much more pronounced and prominent than the others.

(*B*) A confinement of an inflammatory lesion to a particular portion of the kidney substance—for example, glomeruli—does not exist, so that the term glomerulonephritis is wrongly used in such a sense. On the other hand, although there is no kidney inflammation in which glomerular changes are lacking, yet there is no proof that this lesion is the starting-point of all cases of nephritis.

(*C*) I therefore include the degenerative features as inflammatory phenomena, and regard them as evidences of an injury, or the passive features of an inflammation, contrasted with the proliferative and exudative reactive phenomena of the process. But the close association and relation between the passive degenerative and reactive proliferative parenchymatous and exudative changes make it impossible in my mind to ever separate them, the one as non-inflammatory, the other as inflammatory. Pure parenchymatous degenerative lesions, unaccompanied by at least an inflammatory œdema of the parts, do not exist, and it is an artificial stretching of ideas to keep them distinct from the conceptions of the inflammatory process. This conception of inflammation is, therefore, not that of a single either purely passive (Virchow) or purely reactive (modern) process, but an expression of the sum total of genetically related, partly injurious and partly helpful, processes, which are excited by irritants.*

*Compare Ziegler, Ueber den gegenwärtigen Stand der Lehre von der Entzündung, Deutsche Klinik, xi.

Other conceptions suffer, in my opinion, from the inherent weakness and artificiality of too strict classification.

Following the original description by Klebs of glomerulonephritis, it has been the effort of many to establish this as a particular characteristic type of nephritis, and some, like Friedländer[33] and Nauwerck, have gone so far as to speak of glomerulonephritis only then, when the glomeruli alone are affected, and in a characteristic inflammatory thrombosis of the capillary tuft.

On the other hand, Ribbert [34] regards glomerulonephritis as the starting-point of any nephritis, and he therefore classifies any further changes as subdivisions of this uniformly primary anatomical lesion. While he strictly adheres to a division of parenchymatous and interstitial nephritis, he interprets them as subdivisions of the glomerular affection.

These represent rather extreme views, and in my opinion suffer from the endeavor to create types of nephritis either out of stages of a lesion, or from an undue impression with prominent features of the inflammatory process in certain cases.

Degenerative and exudative nephrites are always the result of intense general and characteristic intoxications and infections; above all, the acute exanthemata, particularly during the late stages of scarlet fever, but other infectious diseases as well, furnish a large number of the cases—the severe septic condition of the usual or specific types, septicæmia, pyæmia, pneumonia (the latter not at all infrequently), syphilis, erysipelas, and others. Sometimes the primary focus of infection may be difficult to detect, or may appear insignificant, as in angina pharyngis, tonsillitis, or purulent otitis. But there can be no doubt that severe nephritis may be either associated with or follow these apparently trivial infections. The mouth and ear should therefore always be inspected during life and at autopsy.

Grossly the kidney shows the conditions of simple nephritis intensified. It is larger than normal, firm, bulging, and the surface prominently convex. The capsule stretched, removed with ease, leaves a smooth surface, with an opaque, dusky, reddish-white ground-color, and numerous irregular, small, point-like or streaky hemorrhages. These may occasionally assume such dimensions as to give to the whole kidney a predominatingly hemorrhagic appearance. Sometimes small areas of yellow (fatty) color are irregularly distributed (Fig. 7). On section the kidney is juicy, and discharges readily a turbid, œdematous fluid. The cortex is enormously swollen, pale, and contains irregular hemorrhagic streaks and dots. The normal glomerular rows have apparently, to great extent, disappeared, but the glomeruli are evident in the form of glistening, white, slightly elevated points or minute granules. The intervening tubular substance appears thick and cloudy. The line of demarcation between cortex and medulla is unusually well marked, by a more prominent but dull pinkish-gray (cyanotic) appearance of the medullary portion. Here also a grayish swelling with obliteration of the normal rays is marked. These are the evidences of the well-established forms; and naturally the variations may be great. These depend, first, on the stage of the lesion; secondly, on the qualitative features, degenerative or vascular changes predominating. In the early stages the evidences of inflammatory hyperæmia are much more prominent than later, when degenerative and particularly exudative changes, by mechanical compression, aggregation of necrotic material, and by the general œdematous imbibition of the parts, change the picture from red to gray or yellowish pale, and make the markings gradually indistinct, and cause finally entire obliteration.

Fig. 7.—Nephritis degenerativa exudativa hæmorrhagica, from case of endocarditis septica. A large, bulging, uniformly swollen kidney. All normal markings lost. Demarcation between medulla and cortex obliterated. Smaller and larger hemorrhages unevenly but uniformly distributed over the whole kidney cortex. Interpolated are structureless yellowish-white streaks and patches which correspond to exudative and degenerative (fatty) areas. The reflected capsule œdematous, vessels injected. Weight, 300 gms.

Fig. 8.—Marked cloudy swelling and serous imbibition of glomerular capillaries, leading to fusion and hyaline swelling of the lobules; some increase in number and size of endothelial nuclei. Serous exudate into capsular space, leading to dilatation and to hyaline swelling of the capsular epithelium, which is gradually lifted off the basement membrane and pushed toward the tuft. Few leukocytes in the capsular space. × 260.

Fig. 9.—Tuft of glomerulus with distinct separation into lobules; intracapsular exudation more marked. × 260.

Fig. 10.—Various glomerular, periglomerular, tubular, and peritubular changes in nephritis exudativa et degenerativa, partly represented in Figs. 8 and 9. In addition, glomeruli with marked intra- and pericapsular exudate, with necrosis of one glomerulus; another hyaline. Patchy cellular exudate in periglomerular and intertubular tissue. Tubules in various forms of parenchymatous degeneration and necrosis. In the upper part of the picture tubules may be seen to contain leukocytes. × 125.

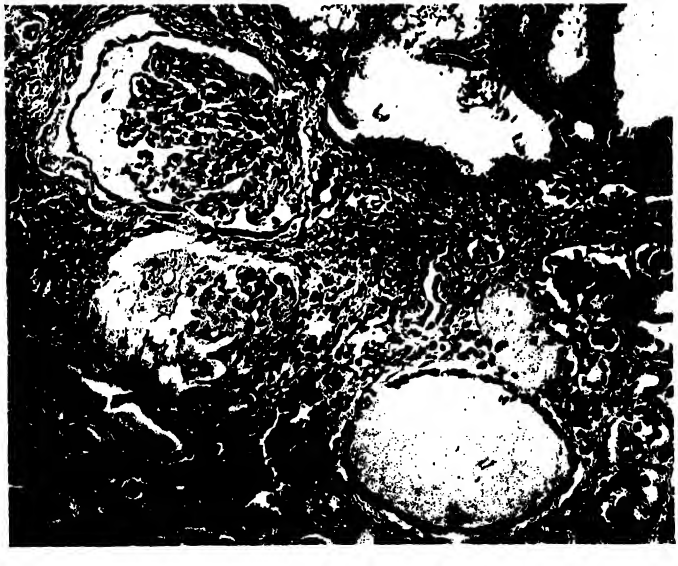


Fig. 11.—In the upper part of the field a glomerulus shows separation into distinct lobules by fusion of capillary loops, with localized attachment to capsule. A glomerulus below this shows compression by exudate and hyaline transformation of the tuft. Thickening of connective tissue. Cystic dilatation of tubule in lower part of field. × 175.

Fig. 12.—Fusion of glomerular tuft by compression of exudate, which leads to its necrosis, and also dilates the capsule. Below it, hyaline (colloid) cast in a tubule. Periglomerular and peritubular cellular infiltration. × 260.

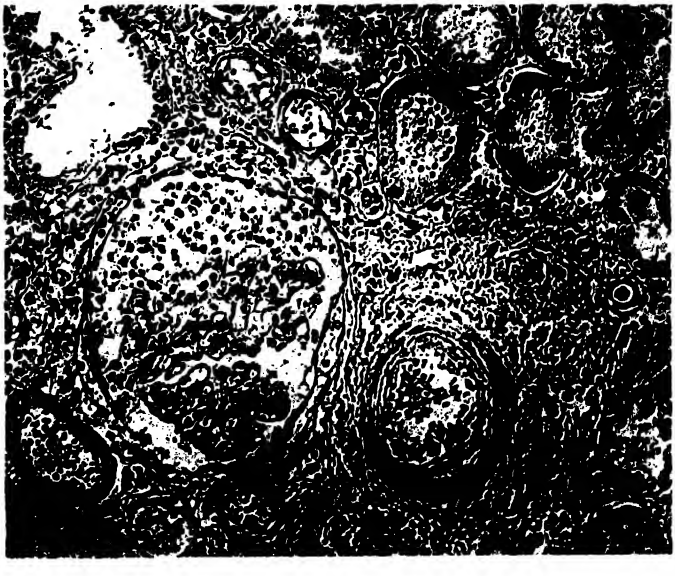


Fig. 13.—Richly cellular (leukocytic) exudate into glomerular capsule, with disintegration of the glomerulus. Similar exudation in surrounding tissue and into the tubules, which show parenchymatous swelling. × 210.

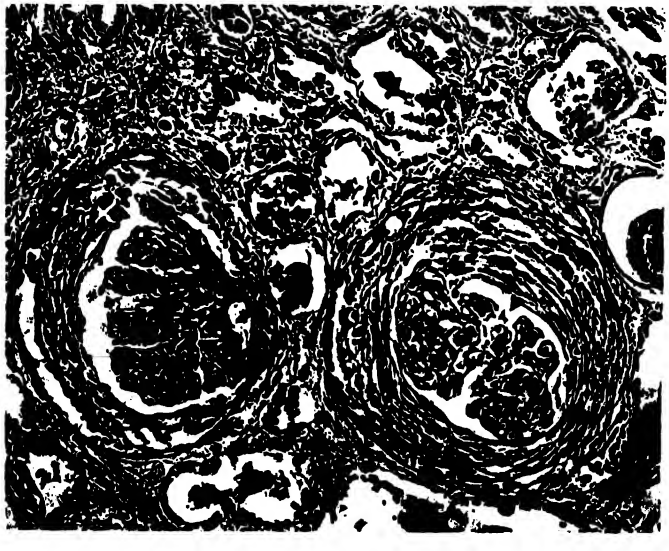


Fig. 14.—Typical capsular epithelial proliferation in glomeruli, becoming gradually flattened and fibrillar, with marked fusion of capillaries, leading to separation of glomerular lobules and final disintegration. × 185.

Fig. 15.—Marked purulent infiltration and staphylococcal emboli in the glomerular loops, which has extended to the periglomerular tissue, leading to necrosis of the whole glomerulus. The surrounding tubules show typical parenchymatous degeneration. × 150.

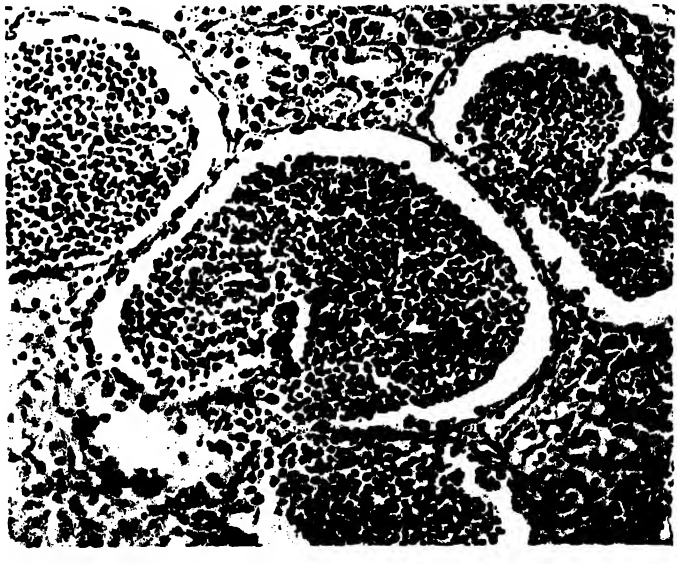


Fig. 16.—Complete purulent necrosis of glomeruli. Capsular space and tubules relatively free. × 200.

Fig. 16*a*.—Topographical picture of nephritis exudativa degenerativa hæmorrhagica. In the upper part of field several glomeruli in state of necrosis. Cellular infiltration of interstitial tissue. Parenchymatous degeneration and necrosis of epithelial cells of convoluted tubules, with marked hemorrhagic exudate into them; one hyaline cast. × 162

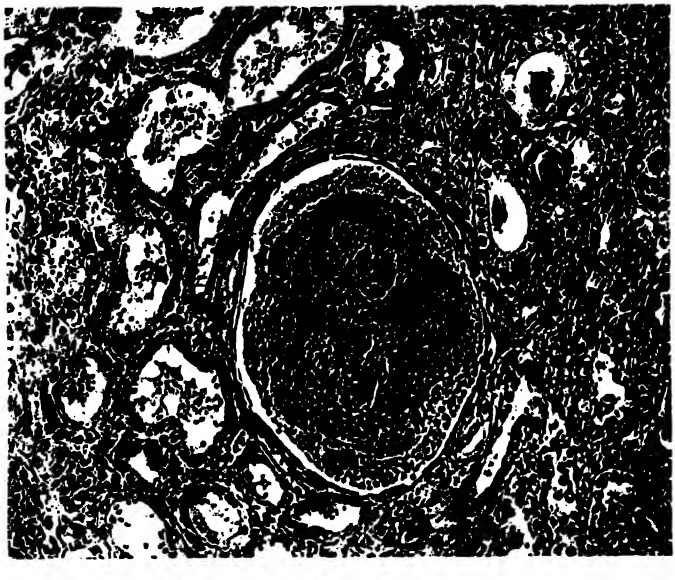


Fig. 17.—Hemorrhagic necrosis of a glomerulus. Necrotic inflammatory cells surround the glomerulus. Hemorrhagic exudate into tubules. × 125.

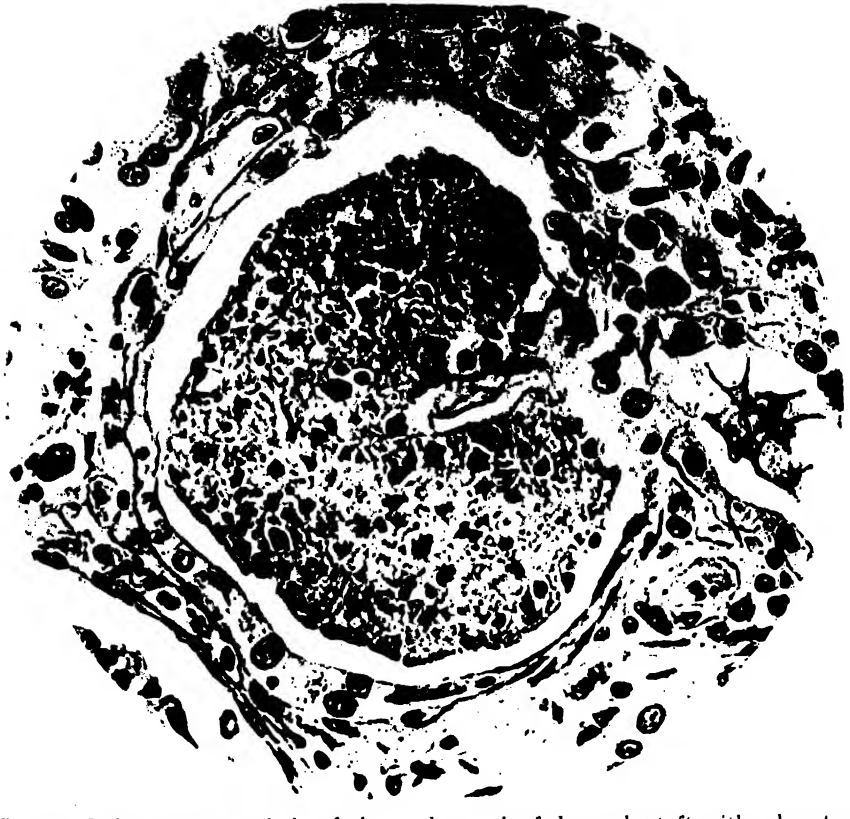


Fig. 18.--Inflammatory exudation, fusion, and necrosis of glomerular tuft, with œdematous swelling of capsular epithelium.

Fig. 19.—Hemorrhagic fusion and necrosis of tuft. The surface still shows few dropsical, swollen, endothelial or epithelial cells. Œdematous swelling of capsular epithelium.

In certain cases hemorrhages occur early and persistently, and therefore give to the whole lesion a characteristic appearance. For the sake of study, we may divide the manifold microscopic processes under the following headings: changes in the glomeruli, changes in the tubular substances, changes in the intertubular substance.

First, the changes in the glomeruli have been well studied and are of the greatest importance, for, as we will see later, the ultimate fate of the kidney depends largely upon them.

The first changes in the glomeruli are degenerative in character and affect the endothelium of the capillaries and the lining epithelium of the tuft. Coincident is inflammatory hyperæmia of the capillaries, rapidly followed by serous imbibition of all the structures of the tuft. In severe cases all of these are well accentuated from the start. In milder cases, von Kahlden[35] found degenerative features the very first phenomenon, consisting mainly of fatty degeneration of the capsular epithelium and capillary endothelium. Even in these milder cases, however, inflammatory œdema into the tuft and into the space between it and the capsule follows so rapidly that it cannot well be separated from the degenerative changes. As the result of both of these—degeneration and serous exudate—the capsular epithelium is lifted off the basement membrane and pushed forward, the epithelial cells of the tuft loosen and desquamate, hyaline swelling, leading to thickening and turbidity of the capillary walls, occurs. As a result of this, fusion of the lobules follows with the characteristic inflammatory accumulation of leukocytes, and their emigration into the tuft and capsule. The appearance of free red cells is frequent. The exudate lies partly in and between the convoluted loops and lobules of the capillaries, but later fills the capsule, gradually compressing the convoluted tuft toward a peripheral portion of the capsule. As

a consequence, the tuft, thus affected, appears primarily large, plump, pale, filling the capsule completely; but later the capsule distends, as the result of pressure from coagulated exuded masses and cell detritus, and leaves the capillaries retracted and less conspicuous (Figs. 8 to 12).

Much discussion has arisen over the question as to whether here proliferation of the epithelium lining the tuft occurs. On account of the complicated pictures in the tuft, it offers particular difficulty.

I do not share the view that this takes place to any extent. Evidently, the initial degenerative changes and the other inflammatory conditions make this impossible. The bulk of the nuclear increase within the tuft appears to me of leukocytic and endothelial derivation (Fig. 13). On the other hand, proliferation of the epithelium of the capsule is a frequent, rather constant phenomenon. It is seen particularly beautifully in scarlet fever, and sometimes in the other exanthemata, severe septic conditions, also in syphilis. Whether it is a very early phenomenon is doubtful. Von Kahlden was never able to observe it in very recent cases. It is certain that it occurs only in well established nephrites. One can observe that gradually rows of large epithelial or epithelioid cells, following the inner circular wall of the capsule, concentrically advance from the periphery toward the lumen. This proliferation usually commences in those glomeruli which have become widely stretched and dilated by free exudate, and in which the tuft has been pushed toward one pole (Fig. 14).

From the opposite direction, this epithelium advances into the capsule, inclosing the exuded masses within it, and gradually assumes a characteristic prominent crescent shape, which the German pathologists have long described under the name of "Halbmond" (crescent) pictures. In some cases it becomes

Fig. 20.—Complete granular necrosis of glomerular tuft, surrounded by coagulated serous exudate. Few swollen epithelial or endothelial cells still visible. × 400.

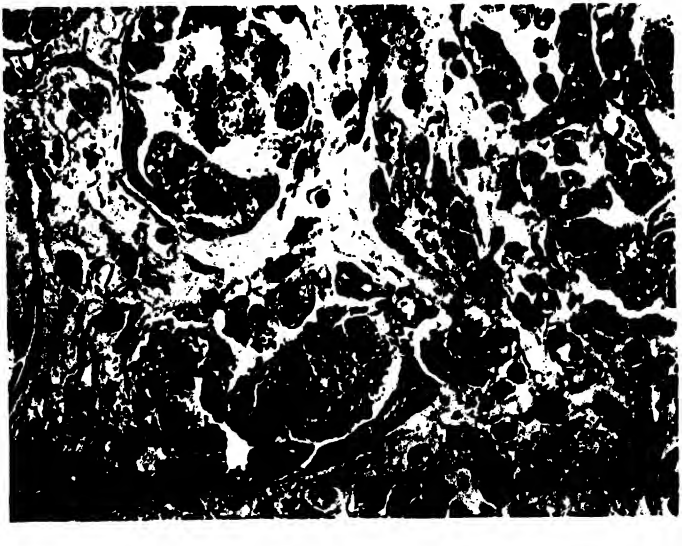


Fig. 21.—Destructive parenchymatous degeneration of tubular epithelium. Fusion of granular cellular detritus into casts within dilated tubules. × 530.

Fig. 22.—High magnification of a tubule, with granular cytoplasmic disintegration and nuclear loss.

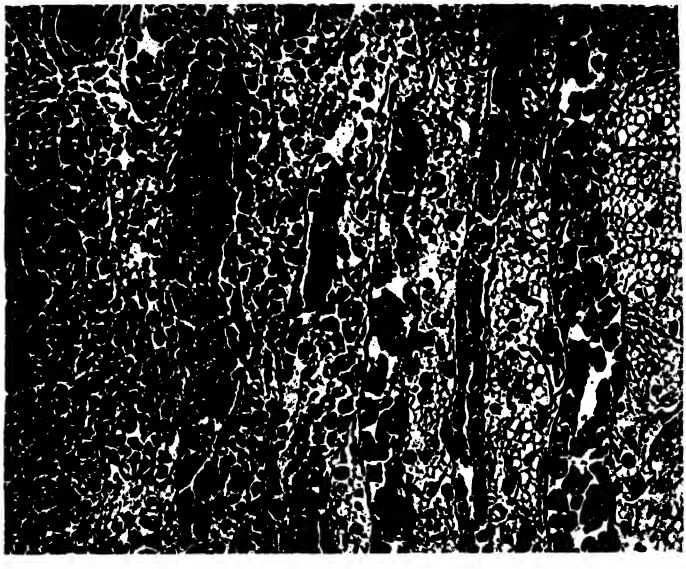


Fig. 23.—Granular cellular masses, leukocytes, and epithelial cells in tubules, with extensive necrosis of these desquamated cells, inflammatory engorgement, and hemorrhages of intertubular tissue. × 225.

Fig. 24.—One tubule with leukocytic exudate, another with epithelial necrotic masses, two others with hyaline formation in tubules.

excessive, replaces the whole of the tuft, and undergoes hyaline degeneration. This epithelial proliferation appears to be an inflammatory phenomenon, excited here, as in the tubules, by the accumulation of necrotic and exuded masses, and fulfils primarily phagocytic-clearing duty, inaugurating fibrous and hyaline replacement. These we will consider later.

Of rarer occurrence are the formation of inflammatory hyaline thrombi in the capillaries, described by Friedländer; and Ribbert observed flattening of the thickened lining epithelium, thereby adding to a compression and impermeability of the vessels already established by exudate and desquamated endothelial cells. Diapedesis of red blood-cells may become very marked, with severe hemorrhages, complicating exudation into the tuft or capsule. In these, rapid necrosis is the termination. When the exudate becomes purulent, the glomerulus meets the same fate (Figs. 15 to 20).

Secondly, as regards changes in the tubules. These are unevenly distributed, usually more intense in the first convoluted portion, and relatively less in the limbs of Henle and the collecting tubules. Senator[35] has pointed out that this is probably the result of the greater concentration of the blood-current, after leaving the glomerulus, which necessarily exposes the epithelium of the convoluted tubules to direct and greater injury. On the other hand, the experimental investigations of Lyon[37] have demonstrated that in certain acute intoxications the ascending limb of Henle suffers most severely. They are the least resistant parts, and show disintegrative and necrotic changes more commonly than elsewhere. The cells, in thus affected parts, show intense parenchymatous degeneration, leading to fatty degeneration and necrosis. Unlike simple nephritis, the tendency is here to destruction and loss of cells. Swelling and turbidity, with loss of cellular outline, are here marked from the beginning, cell masses

fuse, the protoplasm disintegrates entirely, and fatty substances tend to appear in the form of fine droplets; vacuoles appear; the large granules of the cell, by confluence, form necrotic masses, and after breaking of the cell membrane, the detritus is discharged into the lumen of the tubules (Figs. 21 to 24). In severe cases the lining membrane may be completely desquamated (Fig. 28). It is interesting to note, and was first pointed out by Ribbert, that the appearance of fatty substances commences early and primarily in the cells of the loops of Henle, and if we look at such a specimen, one cannot help being astonished at this apparent selective location. Later, however, all the cells undergo the same fate. Changes in the nuclei appear later, but are here of equal severity, leading to their entire loss. They are destroyed either by rapid chromatolysis, with some persistence of the achromatic substance, or the chromatin becomes clumped, solid, and homogeneous, so that the original structure of the nucleus is entirely lost. This condition is known as pyknosis, and eventually results in breaking up into smaller chromatic masses and eventual loss. Finally, nuclei may disappear by a primary peripheral displacement of the normal chromatin masses in the nucleus, leaving its body pale. These chromatin masses are later discharged into the protoplasm of the cell, where they gradually disappear.

Proliferation of the epithelium is here a characteristic and important phenomenon. It is excessive, and goes hand in hand with the necrosis of the epithelium and the accumulation of inflammatory detritus.

For this reason it appears usually more prominent in the lower portion of the tubules, where much of the débris, on its removal, stagnates; less so in the upper parts, but may assume there as great dimensions, if the necrosis of the cells and the accumulation of inflammatory detritus assume any proportion

Fig. 25.—Complete desquamation of epithelium of tubules, with granular contents in lumen of tubules. × 400.

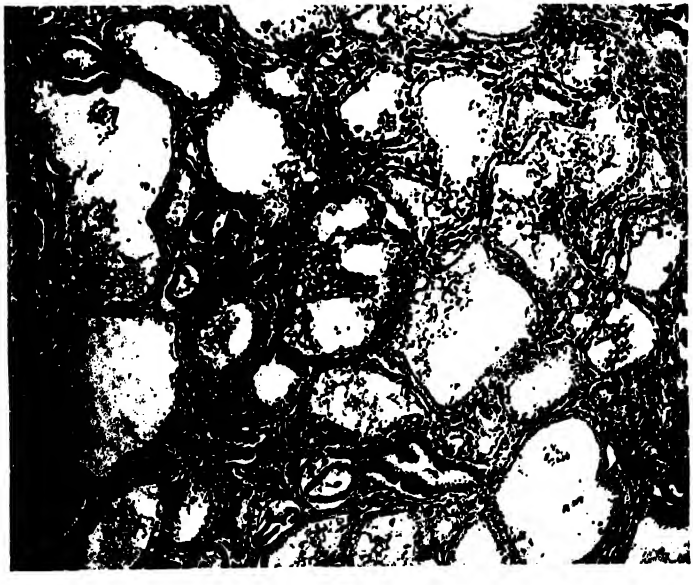


Fig. 26.—Marked dilatation and distention of tubules. × 125.

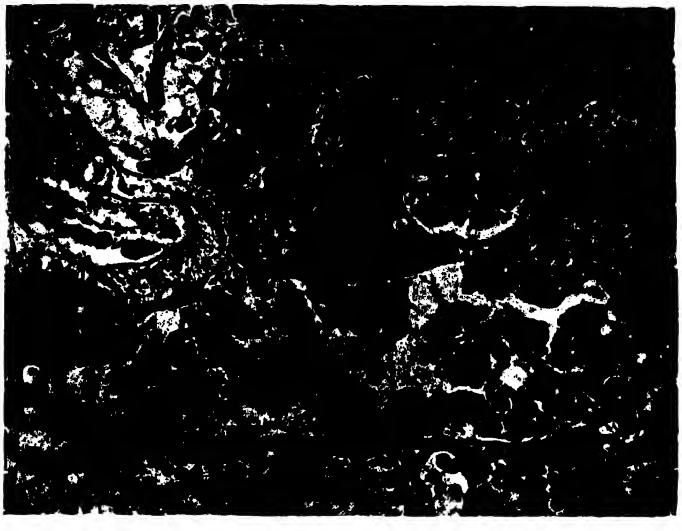


Fig. 27.—Cast formation: Desquamation and proliferation of epithelium; intertubular engorgement. Some of the epithelium pigmented. × 400.

Fig. 28.—Hyaline and more solid colloid casts in tubules. Those containing the casts with peculiar low epithelial cells and considerable dilatation. × 250.

(Figs. 23 and 24). This important fact appears plain from the observations of Lyon, Heineke, and my own. The cells thus derived from the lining epithelium of the tubules differ entirely from the normal in appearance and function. In the lower portion of the tubule they are generally small, cuboidal in nature, growing diffusely within the tubules; in the convoluted parts they are much larger, frequently forming multinuclear giant-cells by fusion or overgrowth. As I said before, their function must be brought into relation to the inflammatory defenses of the tissue. This is indicated, not only by their distinct morphology and abundance of production, but also by the phagocytic power of these cells. Regeneration of typical permanent epithelium does not occur until all inflammatory irritants and products have thus been removed, but then with great activity. The process here outlined cannot but arouse one's great interest and astonishment from a general pathological standpoint. Consider for a moment that highly differentiated epithelial cells, under the necessity of foreign invasion, so to speak, throw aside their higher attributes, and produce an offspring which, not only morphologically, but also functionally, is distinct. This production is continued, as necessity requires, over and over again, until after a time the cells either succumb or have succeeded in removing the cause of their distress. Then, as a more wonderful phenomenon, they are able to reproduce their own original kind; return, in other words, to their former morphological and functional differentiation. In this process are concealed from us some of the most important and fundamental biological laws. If we were able to follow it, we would know what determines proliferation of cells, what determines the functional differentiation, and how some properties may remain potential, to redevelop under favorable conditions. It would be the greatest step toward the solution of tumor growth. I will refrain, how-

ever, from going into theoretical discussions here and return to facts.

The lumen of the tubules contains more than this material; leukocytes, red cells, coagulated albuminous exudate enter partly through their own injured walls, and to some extent are washed down from the glomeruli. As a consequence, the tubules enlarge, so that their lumen is frequently double the size of a normal one (Fig. 26). Gradually the contents are moved toward the pelvis of the kidney, and finally are washed out with the urine, or pressed and fused into casts.

To the latter we must now pay attention. Casts are either cellular or they are homogeneous, pale, transparent hyaline, or, if thicker and more solid in appearance, waxy; finally granular. Not infrequently they may be mixed by the adhesion of cells to a hyaline or waxy ground matrix (Figs. 24, 27, and 28).

The origin of the cellular casts—epithelial, leukocytic, blood-casts, and the granular varieties—can be easily traced to fusion of these substances within one or another part of the tubules. Very difficult and disputed, however, has been the origin of the hyaline and waxy types. A number of investigators believe that they originate from fusion of desquamated epithelial protoplasmic remnants. Others, however, believe that they are the product of an albuminous exudate into the tubules. The formation from fibrin has also been advocated, and finally it is held that they are the product of a specific secretion of hyaline globules of the epithelial cells. The literature on the formation of casts is very extensive, so that it will be impossible to even briefly review all of it.

Doubtless you recall that it was the great anatomist Henle[38] who first discovered this relationship and importance in connection with the inflammations of the kidney. He interpreted them as fibrin coagula. Rovida[39] later thoroughly analyzed them chemi-

cally and demonstrated them as albuminoid bodies. Since then very numerous anatomical and experimental investigations have endeavored to demonstrate their exact derivation and chemical constitution. Physically these hyaline casts are usually under 1 mm. long, and the thickness is between 0.01 and 0.05 mm. Their shape necessarily varies according to the tubes they come from; and on their downward way they are frequently broken or bent. In the kidneys they may be found in all parts of the tubules, but with particular frequency in the loops, undoubtedly on account of the mechanical difficulty of propulsion there. A relationship between albuminuria and cast formation does not seem to exist; and one may be abundant without the other. This fact, as well as their apparent different chemical constitution, has been particularly emphasized by those who do not recognize their derivation from exuded serum-albumin. On the other hand, Weissgerber and Perls[40] and Ribbert[41] are of the opinion that these casts represent a hyaline transformation of exuded albumin. It would be necessary to assume for this a ferment action. Ribbert denies a derivation from desquamated and degenerated cells. Orth[42] also recognizes transudate casts, and in support draws attention to the occurrence of hyaline masses between the tunica propria and uninjured epithelium in some kidneys. But he further believes that the previously mentioned hyaline and colloid globules, which appear in the cells during the process of parenchymatous degeneration, may be discharged, and fuse, with the formation of casts. He calls these "secretion casts." Similar are the views of Landsteiner,[43] who holds that hyaline bodies develop in the epithelial cells as a result of pathological stimuli. They are discharged and fuse to casts.

Ribbert, on the other hand, claims that such hyaline bodies may be observed in healthy kidneys, and that any relation to the formation of casts does not exist. Pfister[44] observed the occur-

rence of granules within the degenerating cells, which responded to the fibrin stain of Weigert, and also in other staining qualities resembled casts. Similar had been the views of Henle, and later Klebs, Israel, and Ernst,[45] who regarded them as fibrin, particularly as they answered to Weigert's fibrin stain. This has been contradicted by Lubarsch,[46] who holds that other substances give similar reactions, and that the diagnosis of fibrin must be made on morphological as well as tinctorial grounds. Much confusion has arisen over the nature and significance of waxy casts. They have been regarded by some as amyloid, on account of certain reactions, but they occur in all forms of nephritis, are of variable reaction, and, in all probability, are not amyloid.

Lyon[47] regards casts as either a coagulation of an intratubular transudate or, in the majority of cases, arising by granular disintegration or colloid transformation of secreting cells.

It appears that all casts are probably not of definite uniform character and derivation. This is made likely, not only by the multitude of observations of their derivation, but more so by their extremely variable morphology and chemical character, as is particularly well shown in their different staining affinities. Sometimes they stain faintly with eosin, sometimes rather deeply; occasionally they seem to have some affinity for basic stains. With iodin they stain from dark brown through all shades to yellow; with methyl-violet, blue, but also violet or pinkish. On the other hand, waxy casts never give the iodin-sulphuric-acid reaction for amyloid, and are better termed colloid casts, to avoid confusion.

I therefore believe that the origin of these casts depends upon several factors, and is inconstant. Epithelial cells, by granular disintegration and subsequent hyaline transformation, can apparently furnish material for their formation, and this process can be directly demonstrated in all stages. That a

colloid secretion is furnished by the epithelium is not probable, but, more likely, that a colloid degeneration or transformation of the cells—as Lyon expresses it—contributes toward them. Finally, it appears that both of these substances may fuse with inflammatory albuminous exudate. We can recognize, therefore, these three factors that enter into cast origin, and as one or the other predominates or may be absent, the character of the cast varies physically and chemically. These views are further supported by the observations of Litten,[48] who demonstrated not only the participation of coagulated epithelial matter, but also the addition of transuded serum-albumin; and Langhans,[49] who saw not only epithelium, but also changed leukocytes and red blood-cells entering into their combination. That in the presence of much disintegrated cell material, ferment action may play a rôle[50] to further change the constitution of these substances, and cause coagulation, seems likely. Ribbert contends that the acid reaction of the urine may be a factor in the coagulation of albuminous matter to casts.

A few words about cylindroids. These, as you know, are pale, long, tortuous, narrow, usually distinctly striated bands or ribbon-like formations. One end is usually rounded, while the other extremity frequently presents a torn, fibrillated appearance. Some hold them closely allied to hyaline casts; others, however, —and I share the view,—believe that they are mucoid threads, which owe their origin either to prostatic secretion or secretions from Cowper's and Littre's glands. They occur, sometimes in otherwise normal urine, in great abundance, but particularly with other mucoid and slimy matter. On the other hand, they do not seem to have any relation to the inflammations of the kidney, and I have never seen anything in kidney sections which resembled them. This makes it probable that they owe their origin to other parts of the genito-urinary tract.

Thirdly, the changes in the intertubular interstitial tissue. This is not only the supporting connective-tissue frame of the parenchyma, but the carrier of blood-vessels, lymphatics, and the nerves. The changes occurring in it are partly dependent on a primary involvement of these structures, but largely also upon the modifying influence which the involvement of one of these parts exerts upon the other. On the other hand, it is influenced in turn by the pathological relations of the neighboring parenchymatous structures. To make this clear: The changes in the blood-vessels bring about, of necessity, alterations in the lymphatics, which again reflect upon the vascular apparatus and the surrounding connective tissue. But, further, while these changes affect the tubules, their disturbances, by necessary interchange, cause subsequent pathological alterations in the interstitial tissue. It will give you an idea how intimately all these various structures are related, and that much of the complex picture of the disease is not necessarily the result of direct injury or invasion, but a subsequent development, the result of disturbed anatomical relations. This accounts, in no small degree, for the great individual variations which we daily meet in all diseases.

The first change which this interstitial tissue shows is inflammatory hyperæmia. This leads to compression of the rest of the interstitial substance, lymphatics, and tubules. Resorption must, therefore, be interfered with from the beginning. Closely following is the development of inflammatory œdema. This must be attributed to slowing of the blood-current, increased permeability of the vessel-walls, and lack of resorption on the part of the lymphatics. This inflammatory œdema leads to imbibition of the connective-tissue structures and, as we saw before, the epithelium of the surrounding tubules. The connective-tissue fibers separate, become stretched, glassy, pale, inflexible; and stagnation of blood-and lymph-streams follows. Then occurs,

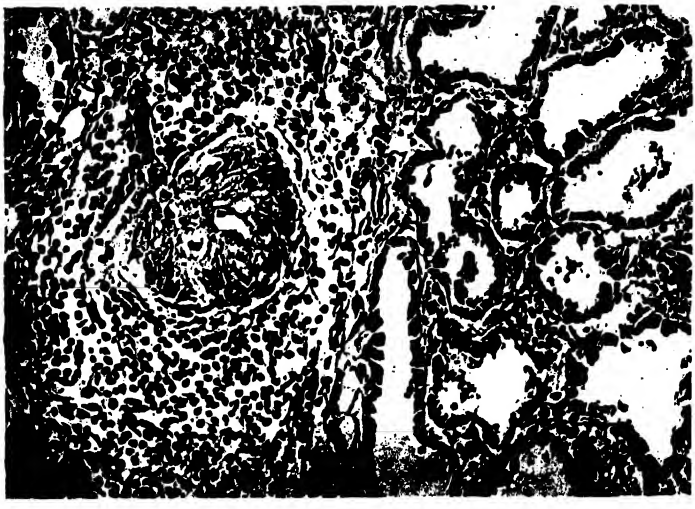


Fig. 29.—Periglomerular interstitial cell infiltration around a hyaline glomerulus. The adjoining tubules much dilated. × 240.

first patchy, but becoming streaky and finally diffuse, a cellular exudation, around glomeruli and between tubules (Fig. 29). The emigrated cells lodge in lymphatics and tissue spaces, producing a lymphangitis and perilymphangitis. They progress within these preformed channels, but also get into the tubules, particularly attracted by necrotic and degenerating portions. The character of these cells varies in different types of inflammations and different stages of the process. Councilman has shown that, particularly in certain of the acute exanthemata, the whole exudate may consist primarily of so-called mononuclear plasma cells and emigrating lymphocytes. Later in the process, as the parenchymatous destruction becomes manifest, polymorphonuclear types prevail.

The exudate contains most always some red blood-cells, and sometimes streaky or diffuse hemorrhages occur. This is noticeable particularly in scarlet fever and in other severe septic infections which have a tendency to marked injury of the vessel-walls. The blood is discharged into the tissue spaces and tubules. In these more severe cases fibrin is also present. Under these circumstances the kidney becomes succulent, softer, and an abundant turbid fluid may be squeezed out on section.

However, these are not the only changes which are prominent in the interstitial tissue. Connective-tissue and endothelial cells undergo cloudy swelling and fatty changes. The latter may become very marked, and lead to accumulation of abundant fat-drops in the interstitial tissue and within tissue and lymphatic spaces. Löhlein[52] regards this as an indication of resorption. The fatty substances are partly ordinary fat, partly doubly refracting myelin substances, and partly a crystalline protagon-like body. I will discuss these matters in detail in connection with fatty degenerative nephritis. It remains to sketch the functional disturbances thus induced.

The severe changes in the glomeruli and tubules necessarily lead to a marked diminution in the amount of urine, sometimes to almost an anuria. The urine thus becomes necessarily high colored, and gradually, as exudate and cellular detritus appear in it, turbid, and, as blood appears, smoky. The specific gravity is high, and this in spite of the fact that the normal urine constituents are markedly diminished. This is not only due to the great concentration of the urine, but more especially to the presence of large amounts of serum-albumin, with nucleo-albumin, the former being derived from the abundant exudate and free blood, the latter from the cellular destruction. Morphologically, such a urine contains all varieties of cells of the exudate: leukocytes, free blood-cells, mononuclear cells, and a large number of desquamated and newly formed epithelial cells. Necrotic cell masses are also present. Casts are very numerous—blood, leukocytic, epithelial, granular, fatty, hyaline, and waxy, with the cellular type predominating. Many of the blood-cells undergo hæmolysis, setting the pigment free, which adds to the characteristic smoky color of the urine.

These evidences vary necessarily with the predominance or absence of these pathological changes, and this leads me to say a few words about these variations and their probable cause.

No doubt you appreciate that what I have presented to you here is a composite picture, subject to many individual modifications. Out of these we can recognize two larger groups: one in which the process is related more particularly and energetically to the vascular apparatus, and one in which the process is predominatingly degenerative and proliferative among the fixed cells of the kidney. As one or the other predominates and influences the later manifestations of the disease, we can recognize that exudative or degenerative and proliferative features predominate, and therefore give to the whole lesion a characteristic

stamp. The cause for this lies undoubtedly not only in the question of quantitative irritation, but in the peculiar affinity which certain invasions have for one or the other tissue. It has been found by Baumgarten, for instance, that the introduction of tubercle bacilli leads mainly to the formation of granulomatous tissue, while the introduction of the toxin without bacteria is followed mainly by exudative processes. The same fact applies to other intoxications and poisons. Snake venoms, for instance, have a greater destructive and, therefore, reactive effect on the vascular apparatus. In scarlet fever this has long been recognized. On the other hand, certain diseases and poisons exert the greatest destructive influence on the fixed cells, and their lesions, and results therefrom, are more evident and dominating in such cases.

Certainly it would be a mistake to endeavor to draw lines of mathematical distinction between these various manifestations. In the end, we are dealing with one or another accentuation of *features* of a nephritis, not with independent distinct diseases. It is only for the purpose of study that we can divorce, or abstract them from the others, thus lifting them above concomitant, correlated, and dependent changes.

FOURTH LECTURE *

The Results and Terminations of Degenerative and Exudative Nephritis. Productive Changes in the Kidney

Gentlemen:

We have followed the nephritic process to the height of its development. What are its terminations? They are three: first, fatal; second, attenuation, with certain modifications in the inflammation, which allows progress in a less brusque manner, and therefore extends over a prolonged period of time; third, latency, with constant danger of exacerbation, and ultimate fatal termination. I have not included recovery in this list, because I consider it extremely doubtful whether actual restitution to integrity ever occurs in severe nephritis, and whether it can ever be regarded as healed or cured, in the sense in which these terms are ordinarily employed. If you recall for a moment the severe destructive changes which we observed in the glomeruli, and the anatomical arrangement of the glomerulus, you will probably agree that the structure has not only been permanently injured and destroyed, but that regeneration to its former state must be out of question. It is true that *cells* may regenerate rapidly, but this requires that the anatomical arrangement of the part has not been lost; it remains confined to cells within established structures. The tuft once destroyed in a glomerulus cannot reproduce a new one. No one has ever seen new glomeruli or tubules form, nor even a new tuft within an old glomerulus capsule.[1] This destruction remains a permanent loss, and the organism must help itself in some other way. Undoubtedly,

* Delivered on February 11, 1909.

many glomeruli have not been injured to such extent as to cause entire obliteration of the tuft. Amelioration of the inflammation will make possible at least some functional activity—in some more than in others; however, the pathological changes in them have at least permanently affected the normal structures, and, while not completely annihilating them, leave them in an injured state, constantly in danger of inflammatory exacerbations. This is particularly unfortunate and dangerous, inasmuch as they are called upon to increase their work in order to compensate those which have been entirely eliminated. This necessary increased functional activity and irritation make them more vulnerable and hasten the ultimate fate of final destruction. In the tubules, as we will learn presently, a very similar state of affairs exists. Indeed, strong evidence has gradually accumulated which points to the fact that many of the so-called primary contracted kidneys, or, better, cases of productive nephritis, are really of the so-called secondary type; that they found their original start in a degenerative exudative nephritis, sometimes fifteen, twenty-four, or twenty-eight years ago, most frequently during the course of a scarlet fever. The recovery in these cases was onlyapparent; the disease continued slowly but progressively, in a manner to which the organism adapted itself, and therefore enjoyed relative health for years, until the disease had finally reached a stage when, as out of a clear sky, a fatal catastrophe occurred. In reality, therefore, of very long duration. Clinicians like Heubner and Dixon Mann have long emphasized such cases. Only recently F. Müller[2] said: "The kidney is a treacherous organ, which may carry latent an injury for decades, to finally cause suffering and death."

Most convincing are the observations of Löhlein,[3] because they furnish an objective anatomical basis for these ideas. I have already touched upon them in the first lecture, but you will

recall that he found that these so-called secondary contracted kidneys are much more frequent than supposed, and may be traced to previous stages of degenerative and exudative nephritis. He also, you recall, drew attention to a type of cases which, having passed through a so-called acute attack, enjoyed relative health, and then suddenly died with all the symptoms of nephritis. In them he found typical productive glomerulonephritis with marked contraction of the organ; the process must have gone on insidiously, but no less perniciously, for years. Similar are the views of Aufrecht.

My own observations in the matter fully corroborate these contentions, and I am of the opinion that at least the majority of cases of late nephritis have been ushered in by previous degenerative exudative lesions, which, having become latent, have been disregarded clinically until their progress has led to a point where the organism is unable to adapt itself. Then it produces manifestations which appear new and sudden, but might have been anticipated long ago. Unquestionably, this has much practical bearing in the matter of prognosis and in the matter of treatment also. One should be very cautious in giving an optimistic ultimate prognosis in any degenerative exudative nephritis, and no doubt many more cases of nephritis could be benefited by treatment if they were more carefully watched for a long time after the evidences of the brusque initial lesions had subsided, and later at intervals. But here, as in other diseases, advice is not sought, and the early stages, still amenable to treatment, are disregarded by the patient, and unfortunately also by the physician. Both usually pay no attention to a disease until it becomes manifest in an entire upset of an organism's economy. Physicians are not always at fault at this. Our diagnostic methods at the best are indelicate, and give information only in severe interferences. But it seems that much of the continued careful

observation has passed out of medicine in a hasty progress. Perhaps the old physician, in spite of his lack of knowledge, may have been unconsciously a better physician in many instances. His close, constant, and friendly association with patients, whom he frequently saw and consulted with, allowed him perhaps to form much earlier and better opinions of expression of disease than we are now able to attain with our hasty, purely objective methods. Much used to enter into the legitimate practice of medicine which now has passed away for lack of time, or has been consumed by the charlatanism of schools, and exaggerated by uneducated, unrefined followers. Dilettantism and notoriety to-day march under the flag of broad scientific knowledge and business methods. People forget that the human mind can only do relatively few things thoroughly and reliably, and, therefore, that in science and art, unlike business, quantity never goes with quality. Nowhere are careful, painstaking, and long-continued observation and treatment more strongly indicated and of greater importance to the patient than in nephritis.

We shall now proceed to consider in detail the further changes in the kidney, commencing with the time we reached at the end of the last lecture.

After the processes of parenchymatous destruction and exudation have attained the height to which we traced them, there occurs, provided that the individual does not die, a relative standstill. By this do not misunderstand that things halt entirely, but the process has arrived at a point where rapid progress and uniformity of degenerative and exudative phenomena stop and evidences of regression and attenuation become visible, gradually leading to new pathological processes, which give to the whole a greater variety of pictures. This depends probably upon complex qualitative as well as quantitative changes within the kidney and the irritant. It would lead me

here too far to enter into a detailed discussion of this question, but I will only indicate to you that this must be attributed, first, to the changes which the inflammation has produced in the tissues of the kidney and in their anatomical arrangement. Into this naturally enter the qualitative changes within the cells and mechanical factors due to the rearrangement of the parts. Second, owing to the changes in the irritant brought about by the inflammatory condition of the organ, much of it has been directly destroyed, or at least altered. Both these points are complex and intricate, and involve many other problems, and I therefore cannot fully discuss them within the scope of these lectures. Suffice it, therefore, if you appreciate that the inflammatory alterations in the structure of the kidney and the concomitant changed relationship to the inflammatory irritant have drifted to a point where the original response of the tissues to the invasion necessarily ceases and undergoes decided modifications. These modifications in the inflammatory process are expressed in two main changes: first, lessened exudation; and, second, fatty degeneration and infiltration of the remaining parts. They result from obliteration and blocking of the normal paths of nutrition and resorption. Consequently nutritive disturbances now commence to control the picture, associated by degrees with inflammatory exacerbations and remissions, and, as the substance wastes, more or less extensive productive changes.

We shall deal with these changes in the order here enumerated. First, then, the nutritive disturbances. These manifest themselves in various degenerative processes, which either were originally absent or less prominent. Colloid and hyaline bodies appear in great number within the disintegrating parenchyma cells; autolytic processes, undoubtedly due to ferment formation from broken-down cells, become conspicuous; but the fatty changes are apt to supersede all others in prominence. They

soon give to the whole type of nephritis a characteristic appearance. As the result of these various degenerations, all of which go along with swelling of cells, the kidney as a whole enlarges. This is further due to the difficulties in resorption and nutrition of the parts, to capillary and lymphatic obliteration, which allows broken-down material to collect and stagnate. It is also added to by the presence of inflammatory œdema, and the occasional exudative exacerbations. All of these contribute to a gradual but very marked increase in the size of the organ and an obliteration of its normal markings. These give way to a more uniform, anæmic, yellowish-pale color, interchanging with areas of vascular injection where the process is exudative or productive, or where, due to obliteration of old normal channels, compensatory dilatation of vascular canals has occurred. At this point of the process the capsule still strips easily, the surface bulges very prominently, as so, on section, does the cortex. The normal markings appear lost or much distorted. The glomeruli are pale and glistening, the medulla dull pale yellow in color, and the line of demarcation between it and the cortex poorly accentuated. In short, it presents the kidney now spoken of as chronic parenchymatous nephritis, or large white kidney; better and more correctly, as I termed it at the beginning of these lectures, the degenerative fatty nephritis. Inasmuch as these fatty substances play such a rôle, we must have a clear picture in our mind what they are, and what is their derivation and significance. Here we enter another very much disputed and much fought over ground of general pathology. You must, therefore, be content with a short summary of the situation.

You are aware that Virchow[4] originally distinguished between two types of fatty changes: degeneration and infiltration. In the latter he assumed that the fat was brought to the part, while in the former occurred a direct transformation of the protein

portion of the protoplasm into fat. This involved, then, an active and much more severe permanent destruction of the protoplasm, while infiltration was passive. Support of this idea came in the celebrated observations of von Voit and Pettenkofer,[5] later followed by others, particularly Bauer and F. Hofman, and followed by the critical review of Pflüger.[6] The latter demonstrated that, although a direct transformation of protein into fat cannot be denied, there is no sufficient proof that this actually occurs. If at all possible, it seems most probable by a primary splitting off of carbon-poor decomposition products, with a following synthesis.

For these reasons, and particularly on account of gradually accumulating experimental evidence, the idea of fatty degeneration became gradually replaced by that of fatty infiltration. It is particularly to Rosenfeld[7] that we owe the most convincing testimony in its favor. He determined the ether extract of normal organs and compared it with that of fatty ones. He and Rumpf[8] observed a variable but decided increase from 25 per cent. to 30, 40, 60, and, in phosphorus-poisoning, even 75 per cent. These large percentages appeared to Rosenfeld as only ascribable to infiltration, and he found the proof in the following ingenious experiments: If an animal is made practically fat-free by starvation, and then fed with a foreign, easily recognizable fat, as mutton fat, cacao-butter, line oil, this may easily be detected in the normal fat depots of the body. Now, if such an animal is poisoned with phosphorus, or some other substance leading to marked fatty degeneration, the fatty degenerated organs are found to contain this foreign fat. If, on the other hand, such animals were simply starved and then poisoned, fatty degeneration did not occur. Lebedeff[9] has made similar observations in starved human beings, with the same result. The previous investigations of Lusk[10] and his pupils on phosphorus-

poisoning had already demonstrated the infiltrative character of these fatty changes, and he interpreted them as an attempt on the part of injured cells to keep themselves alive. He therefore speaks of sugar-hungry cells.

An interesting observation was also made by Fischler,[11] who carried soap solution through excised kidneys, and obtained in this way the picture of fat degeneration. He accomplished the same by using blood, soap, and glycerin. From this it was concluded that the fat is brought to the parts in soluble form.

Rosenfeld found, further, that there exists a distinct relation between the glycogen content and fat degeneration. The latter does not occur in the presence of the former, and if glycogen is administered to animals poisoned with phloridzin, the fat degeneration diminishes. He interprets this similar to Lusk: Fat and glycogen furnish fuel for the purpose of defense against toxins, and compensate, therefore, a lost protoplasmic portion of the cell. Rosenfeld, therefore, speaks of fat regeneration, instead of fat degeneration.

Now, pathologists have always hesitated to accept the idea of pure fat infiltration for all fatty changes in organs, and mainly on morphological considerations. You know well that the appearance of fat in cells goes along in certain cases, just as Virchow observed it, with protoplasmic destruction, and again with relatively good preservation of the cell constituents. For the first, pathological anatomists have retained the term of fatty degeneration, and for the second, fatty infiltration. Very soon evidence accumulated which again brought new support to these old but perfectly justifiable conceptions. In the first place, it was found that the apparently very clear conclusive observations of Rosenfeld and others had notable exceptions, inasmuch as in some fatty degenerated organs—the kidneys, particularly—the fat content was not only not always increased, but occasionally

actually diminished! How can this be explained? Explanation of this phenomenon came from another source.

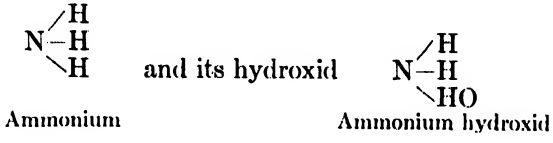
If organs are kept under entirely aseptic conditions, there occurs, as you know, a post-mortem softening. This is especially well illustrated in certain inflamed organs, particularly the lungs, which are rich in exudate. This softening, or autolysis,[12] is accompanied by the appearance in the cells and tissues of an abundance of granules, somewhat similar in morphological appearance to the changes we observe in the process still called fat degeneration and in late parenchymatous degeneration. These small fat-appearing droplets differ, however, in certain important physical and chemical respects quite markedly from the ordinary neutral fat, *i. e.*, the combination of glycerin with a fatty acid radicle. Physically, these substances are characterized by double refraction of polarized light; chemically, by a marked difference in constitution from ordinary fat, and decomposition with frequent formation of glycerin phosphoric acid. While such bodies have been known for a long time and been called collectively "myelins" by Virchow, they assumed now a new light and importance, and have recently been the field of much active investigation.[13] They include substances, the most familiar of which are lecithin, protagon, cholesterin. They have also become known under the name of lipoids, a term introduced by Kletzinski fifty years ago, and reintroduced by Overton. Common to all of them is solubility in ether, alcohol, chloroform, benzol. I cannot enter here, of course, into a detailed discussion of these bodies, but I will illustrate their general chemical relations.

Our knowledge of the chemistry of these substances is still very uncertain, which is largely due to the fact that it has been extremely difficult to isolate them in the pure state. The entity and constitution of some of them, at least, are, therefore, still doubtful and uncertain.

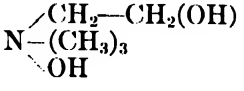
According to the investigations of Thudichum and Bang, we may classify them first: As phosphatides, *i. e.*, lipoids containing nitrogen and phosphorus. To this group belong the lecithins and the related bodies, kephalin in the brain, myelin and paramyelin and sphyngomyelin, occurring also in the brain, in egg yellow, in red blood-cells, and in the suprarenals. These represent mono-amido-mono-phosphatides, mono-amido-diphosphatides, di-amido-mono-phosphatides, and tri-amido-phosphatide, the latter a substance occurring in the kidney.

Their chemical constitution is perhaps best illustrated in the lecithins. In order to trace this structure we have to synthetize the decomposition products.

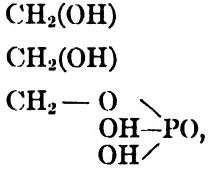
Commencing with ammonia, with which you are all familiar,



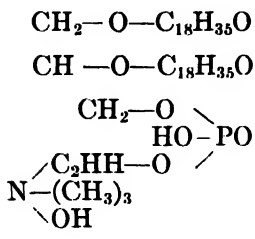
we may obtain by simple substitution a compound known chemically as trimethyl-oxy-ethyl ammonium, or more frequently as cholin, an ammonium base, as follows:



This base may combine with glycerin phosphoric acid:



in which two of the hydrogens have been replaced by two fatty acid radicles, say of the stearyl group:



and we then obtain the distearyl-lecithin. It will be plain from this formula and development that there is more than one kind of lecithin, depending upon the kind of fatty acid radicle in the glycerin-phosphoric-acid group of the compound. We, therefore, have also palmityl and oleyl-lecithins, and Thudichum regards it as possible that two different fatty acid radicles may enter into the combination, thereby increasing the number of possible lecithins.

All of these substances occur in animal cells in abundance, and their decomposition products are found normally in traces in the urine,[14] but under abnormal conditions, particularly in certain metabolic and nervous disturbances with toxic symptoms, cholin and glycerin (organic) phosphoric acid have been found much increased in the urine.[15]

The second group is made up of nitrogenous but phosphorus-free lipoids, the so-called cerebrosides, and related to the glycosides, which form constituents of the so-called protagon.

The third and very important group is represented by the non-nitrogenous and non-phosphorized cholesterins, which belong to the terpenes. These are of very great interest, not only on account of their wide occurrence in the animal and vegetable kingdom, as the so-called phytosterin, but because they particularly have acquired a very great rôle in the problems of fat degeneration and fat infiltration. The elder Beneke drew attention to the abundant occurrences of cholesterin many years ago,

but not until recently has this importance been properly valued. Chemically, it has the formula $C_{27}H_{46}O$, and is a monovalent, simple, unsaturated, secondary alcohol, containing four saturated hydrated nuclei. The chemical constitution of cholesterin stamps it evidently as complicated terpene, *i. e.*, isomeric hydrocarbon of the general formula $C_{10}H_{16}$. It has, therefore, no chemical relation to the previously mentioned substances or the fats. Related to the cholesterins in the animal body are certain decomposition products, as kaprosterin, formed in the gut from the cholesterin of the bile, and further isocholesterin, found in lanolin. Part of the cholesterin secreted by the bile, however, seems to be reabsorbed by the gut, similarly to the bile-pigment.

As an example of its wide distribution through the animal body, I might mention that it apparently forms an outer zone to many cells, and acts antagonistically to cell solvents. Thus, in erythrocytes it is, according to Ranson, distinctly so to the hemolytic action of saponin.[16] The origin of cholesterin in the body is so far unknown; it may possibly be derived from the vegetable phytosterin. Its natural history in the body is also unknown; but it occurs in combination with fatty acids, and particularly as esters. Protagon, which I mentioned before, has had a very disturbed history. First discovered by Liebreich in 1865, and pronounced an entity, it appears now to be mostly a mixture of phosphorized and phosphorus-free lipoids, particularly sphyngomyelin and phrenosin. A protagon-like substance occurs in nephritis, according to Löhlein[17] and others, in crystalline form in the intertubular tissue and the lymphatics. It is there probably derived from an abundant disintegration of cell protoplasm. It is doubly refractive, and gives the sudan III fat stain, soluble in alcohol and insoluble in acids and alkalis. Panzer,[18] however, has shown that this is probably also an ester of cholesterin with fatty acids.

It has developed, therefore, that fat-related substances may appear during the disintegration of the protoplasm of all cells, and that some of these, on further decomposition, may yield neutral fat. This, under such conditions, is therefore not necessarily brought to the parts from distant depots.

Now, what does all this represent, and what is its relation to fat degeneration and fat infiltration?

In the course of investigation into this problem some very interesting points developed. Rosenfeld as the first drew attention to the fact that the microscopic appearances and valuation of fat contents of an organ are unreliable, and that, therefore, chemical and morphological results do not cover each other in fat determination. Healthy and fatty kidneys may not show their fat contents at all, even if this amounts to 23 per cent. More curious, however, is the fact that kidneys of the same fat contents (17.9 to 18.2 per cent.) may appear at one time healthy, at another extremely fatty. Kidneys with even a diminished amount of fat, say, 16 per cent., may seem to us at times extremely fatty. That this is not peculiar to the kidney was shown by Bossard and Schmoll and Rosenthal.[19] The latter could not demonstrate morphologically with osmic acid and sudan any fat in cheesy tuberculous masses, while ether extracted considerable amounts of soap and cholesterin. Klotz,[20] from Adami's laboratory, has only recently pointed out that at least part of the myelins in the kidney exist as soaps of oleic acid, and that such fatty compounds are not readily demonstrated by the ordinary staining with sudan III, but can be obtained by extraction with alcohol. It is, therefore, evident that the presence of fat and fat-like substances may not always be visible; on the other hand, may become visible, with relatively small quantities, not exceeding the normal. From the foregoing it follows that the morphological appearance of fat in the organs means not neces-

sarily increase in fat, but a molecular physical deconstitution of the cell, whereby fat originally contained and concealed in the structure of the protoplasm appears free to us. Kraus,[21] and particularly Albrecht,[22] whose ideas I have already presented in connection with parenchymatous degeneration, assume for its explanation that protoplasm exists normally as a fluid pulp, an emulsion, which contains fatty substances so finely divided that they are invisible. Kraus draws attention to the fact that neutral fluid fat does not readily emulsify, but does so as soon as some fatty acid is added. This is explainable by the supposition that fluid fat is a solution of fatty acid, whose molecules are equally distributed, as in all solutions, between those of the neutral fat. If this mixture is brought into contact with an alkali, these molecules diffuse into it and form soaps, which unite as a honeycomb (Bütschli), inclosing within it the fluid fat in the form of drops. Albrecht's "tropfige Entmischung," or myelinic deconstitution, which we have reviewed, would be of a similar nature, although it also includes important changes in the protein constituents of the protoplasm.

The old conception of Virchow, who spoke of a direct transformation of protein into fat, has been discarded, therefore, and Kraus has reintroduced the term fatty metamorphosis, by which is understood a physical deconstitution of the cell protoplasm, with the liberation of fat-similar substances.

A different view, however, is entertained by Aschoff,[13] who still regards the vital fat processes as infiltrative in character. In favor of this, he puts forward the coexistence of isotropous and anisotropous drops in the same cells, the occurrence of anisotropous substances in cells which show no evidence of degeneration, and particularly the resorption of anisotropous drops by the endothelial lymph-cells of the gall-bladder in long-continued bile stasis; he holds, further, that in abscess formation

and during degenerative inflammatory lesions, as in long-continued nephritis, cholesterin is set free, and either replaces the glycerin with the formation of lipoids, or is taken up by cells as completed cholesterin ester with other neutral fat. He therefore speaks of two groups of fat infiltrations: one, the glycerin-ester-fat infiltration, and the other the cholesterin-ester-fat infiltration. Aschoff differentiates these changes definitely from the so-called postmortem or autolytically originating myelins. The latter, he states, almost always lack anisotropism in contradistinction to the intravital forms. They are not fatty in reaction, and therefore lack the characteristic stains of these substances with sudan III, Scharlach, Nileblue, and osmic acid. But he admits that during autolysis fatty substances of the glycerin and cholesterin type, which were stored in the cells during vital processes, may appear.

There are one or two other points which deserve consideration.

Rubow[23] showed that the percentage increase of fat in the fattily degenerated heart was relatively very low—1.6 per cent. of the moist, 8 per cent. of the dry, muscle substance, amounting to only about 3 per cent. of the fresh muscle, not more than 5 to 9 gm. for the whole heart. Many times it is less. These figures, Rubow holds, can be explained perfectly on the strength of the normal fat contents of the blood (0.1 to 1.4 per cent.), which have not been normally taken up by the injured protoplasm of the cells. As reason for this inability of fat reabsorption by the cells he regards diminution of alkalinity of the plasma. Contributory evidence to this view may be gained from the fact that an increase of acid production has been actually noted in conditions that are very apt to be associated with fatty changes, and that fatty acids are formed during autolysis. Rubow also regards the fatty cell as an injured cell, which, under toxic

influences and a perverted metabolism, produces more acid and probably discharges less. As a result, diminished alkalinity of the cell plasma follows, with inability of fat absorption. Oswald[24] has pointed out that the ideas of Rubow are really not opposed to those of Rosenfeld, inasmuch as it may be supposed that the blood leaves its fat in the degenerating organs to later carry more fat to it from the distant fat depots of the body.

Now, to sum up: From the foregoing it appears that the occurrence of fat in the organs is not of uniform character, and also not of uniform derivation. It may occur first as a transportation of material to cells for the purpose of supplying an easily combustible substance, or, I take it, as a compensatory process to relieve a loss of protoplasmic parts of the cells, which takes place either as a direct destruction, or by quantitative interferences with the cell nutrition, as during inactivity and simple atrophy of organs. Whenever, in such cases, restitution of protoplasmic material becomes impossible, fat is substituted. This accumulation is aided, undoubtedly, in many cases, by inability to burn fat properly. The nature of this fat is largely neutral, isotropous fat glycerin esters. But when this process becomes associated with, and takes place under, conditions leading to rapid cell destruction, it has added to it anisotropous cholesterin esters and other lipoids which either originate in the cell itself or are brought to it from other cellular sources.

On the other hand, in severe degenerations, necrosis, and autolysis of cells, there occurs from the start a severe internal revolution within the protoplasm of the cell, leading to general disorganization of the latter, with the setting free of fat-related substances; these, on further decomposition and re-synthesis, may later give rise to neutral fats, and lead to fat infiltration of other cells.

Fat infiltration and fat metamorphosis are then two inti-

mately connected and related conditions, which depend either on the existence of living cells or on dead or dying and disorganizing cells. The complicated nature of nutritive disturbances in organs makes a combination of both of these at times probable, and the diminished alkalinity of the blood may well be an influencing factor.

Under normal conditions a moderate degree of fat infiltration in the kidney has been noted by von Hansemann, and we can easily conceive of this. But, on the other hand, the myelinic disintegration of cells, and the occurrence of protagon, cholesterin, and related bodies in considerable amount, must always be of pathological origin.

Bearing in mind the experiences of this excursion, and to return to our morphological considerations, you will be in a position to appreciate the great individual variations which the kidney under consideration may present. The fat may either be recognizable in patches, streaks, or cover larger areas; it may be confined to certain parts of the tubules, particularly the loops and proximal end, or it may be diffuse, involving the whole tubule, although in varying degree. In the beginning of the process, fat appears in the peripheral portion of the cell near the tunica propria. While these changes are more prominent in the epithelium of the tubules, they may sometimes reach a high degree in the glomerulus.

I turn now, secondly, to the further events which take place in the glomeruli and tubules subsequent to the inflammatory changes with which we have already become acquainted.

In the glomerulus we had, you remember, degeneration of the lining epithelium and endothelium of the tuft, with proliferation of the latter, exudation within it and into the capsule, and at times proliferation of the epithelial cells advancing from the periphery toward the center. The whole tuft becomes thus

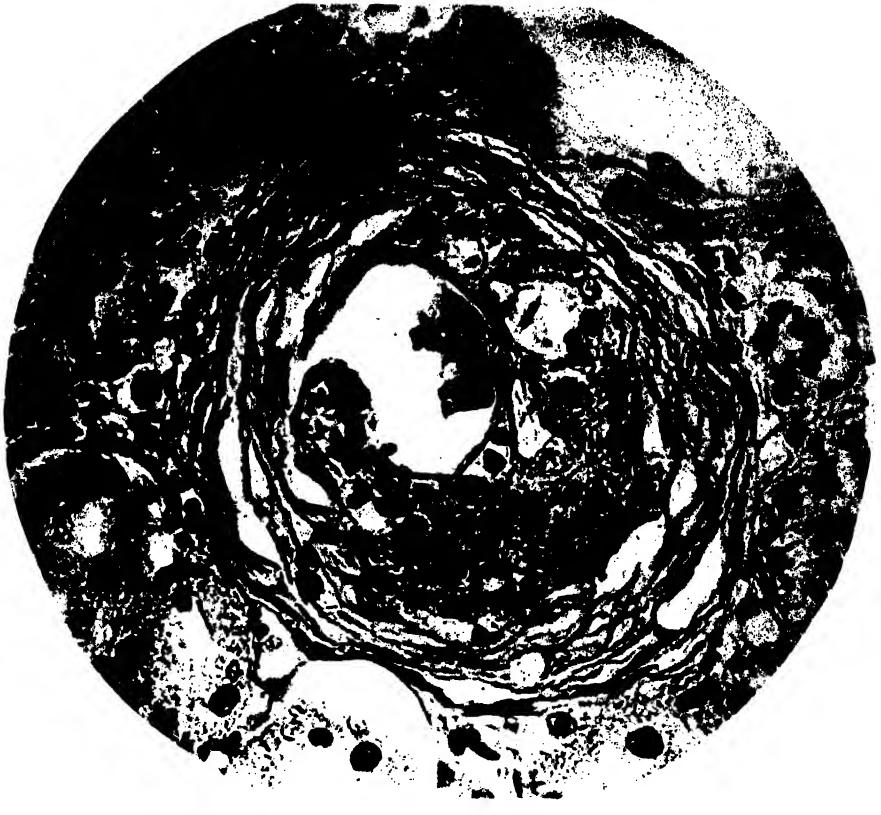


Fig. 30.—High magnification of glomerulus, showing lesion advanced to that of Fig. 14. The flattened, fibrillar, capsular cells are seen to fuse with the cells of the atrophic tuft. Few unusually large capillary loops show in cross-section.

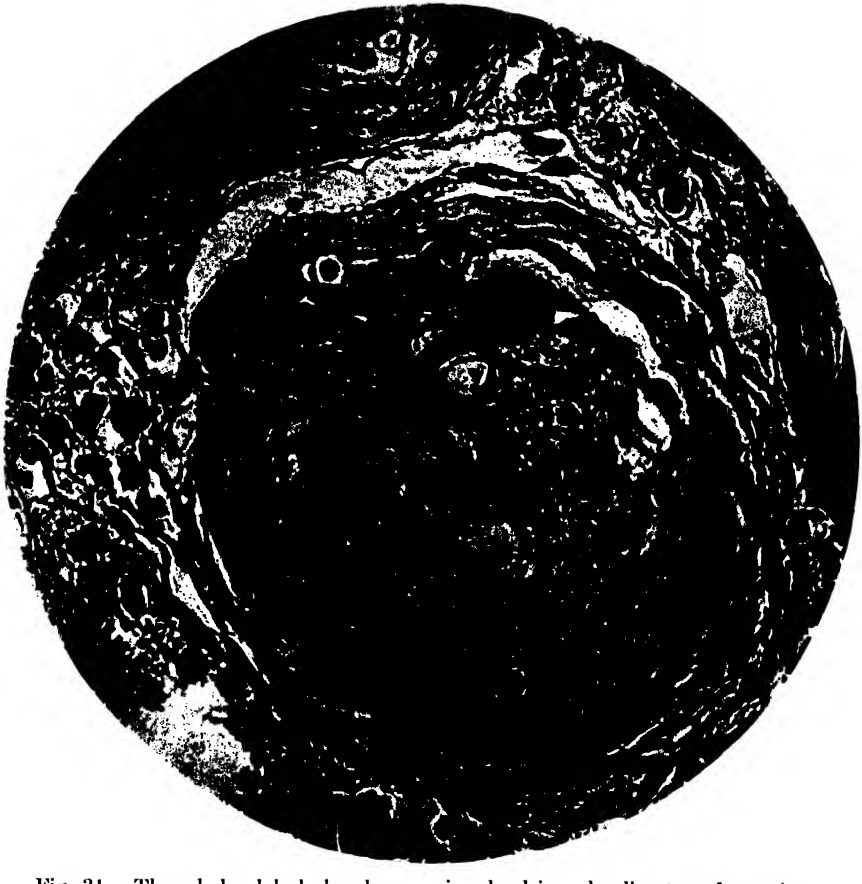


Fig. 31.—The whole globule has become involved in a hyaline transformation.

Fig. 32.—Completed hyaline transformation of a glomerulus with few nuclear remnants. Surrounded by very cellular fibrous tissue.

impermeable. Inflammatory thrombi form within the capillaries, while the cellular exudate fuses with necrotic cellular material and unites the capillary lobules of the tuft and the capsule to a mass. This leads to several results. If the tuft has been shut off from all communication with afferent and efferent vessels, it necessarily disintegrates rapidly, so that its parts break off into fragments and are washed away. If, however, some communication with the outside vessels has been retained, a rather irregular destruction of the glomerulus follows: and some of the still permeable capillaries, particularly near the hilus of the glomerulus, undergo compensatory dilatation. The endothelial cells of these capillary walls swell, while those of the collapsed areas undergo fusion. Capillary lobules are thus obliterated and disconnected from the still permeable portions of the tuft, and fall to one side, to undergo rapid disintegration. Finally, the whole of the tuft filled with endothelial nuclei and hyaline masses and some leukocytes, breaks up into disintegrating lobular remnants, and the capsule collapses.

Where the capsular epithelium has undergone marked proliferation, these cells become flattened, stringy, fibrillar in appearance, fuse with the other cells of the tuft, or, stagnant, retained albuminous exudate to hyaline material. It is possible that endothelial cells of the obliterated tuft may take part in a similar fibrillar and subsequent hyaline transformation (Figs. 30, 31, 32). The destruction of the glomerulus and the Malpighian body is usually not so violent. It may result from fibrinous adhesion of the capillary loops to each other and to the epithelium of the capsule. Löhlein considers adhesion by desquamated capsular cell detritus sufficient. Thus immobilized, a gradual connective-tissue synechia of capsular connective tissue and glomerulus occurs. The connective tissue grows into and separates the fused glomerular lobules. Ziegler, Engel,

and Herxheimer have drawn attention to similarity of these changes with those observed in serous membranes.

Again in protracted, less brusque cases, the glomerular lobes are transformed by hyaline swelling of the loops and endothelial and possibly epithelial proliferation into a compact, plump, first cellular, then hyaline, body. Amyloid material is deposited in the capillary loops, particularly in constitutional diseases, associated with hyaline infiltration of other organs and vessels. According to Wichman and Martland, amyloid material infiltrates the parts, while the cells are not transformed into amyloid, and Hueter finds the amyloid deposited within the lumen of the capillary vessels.[25]

Other processes may also lead to hyaline transformation of the Malpighian body, as the result either of lack of proper blood-supply of the glomerular tuft or, as Ponfick believes, as the result of stagnation within and obliteration of the convoluted tubules. In such events the epithelium and endothelium of the tuft become pale, turbid, swell, and fuse to a structureless, hyaline body. This is occasionally initiated by œdematous imbibition of the parts, so that the glomerulus fills the distended capsule. A common event is connective-tissue invasion from the capsular tunic, which pushes before it a gradually atrophying capsular epithelium (Fig. 38). According to some of Dr. Milne's observations, this seems to be the case in glomeruli where originally the exudate lifts the epithelial cells off the basement membrane and pushes them before it toward the tuft. Later, this exudate is replaced by gradually thickening capsular connective tissue, which occasionally still shows toward the tuft a very thin, almost endothelial-like, cellular lining (Fig. 8 and Figs. 39 and 40).

Similar is the fate of the glomerulus in cases when, as we saw before, only a portion of the tuft has been firmly attached by

Fig. 33.—In one glomerulus, inflammatory attachment to capsule, with localized periglomerular thickening; increase of endothelial nuclei in both glomeruli. Dilatation of capsule. × 185.

Fig. 34.—Various stages of hyaline glomerular replacement. Hyaline casts in tubules. × 200.

Fig. 35.—One glomerulus with complete hyaline atrophy. Hyaline change in a glomerulus commencing in the part attached to capsule. × 220.

Fig. 36.—Complete hyaline atrophy of a glomerulus. In the neighborhood a very much thickened and almost obliterated vessel. × 400.

Fig. 37.—Advanced fibrous invasion and replacement of a glomerulus. An adjoining relatively healthy glomerulus in compensatory functional hypertrophy. × 200.

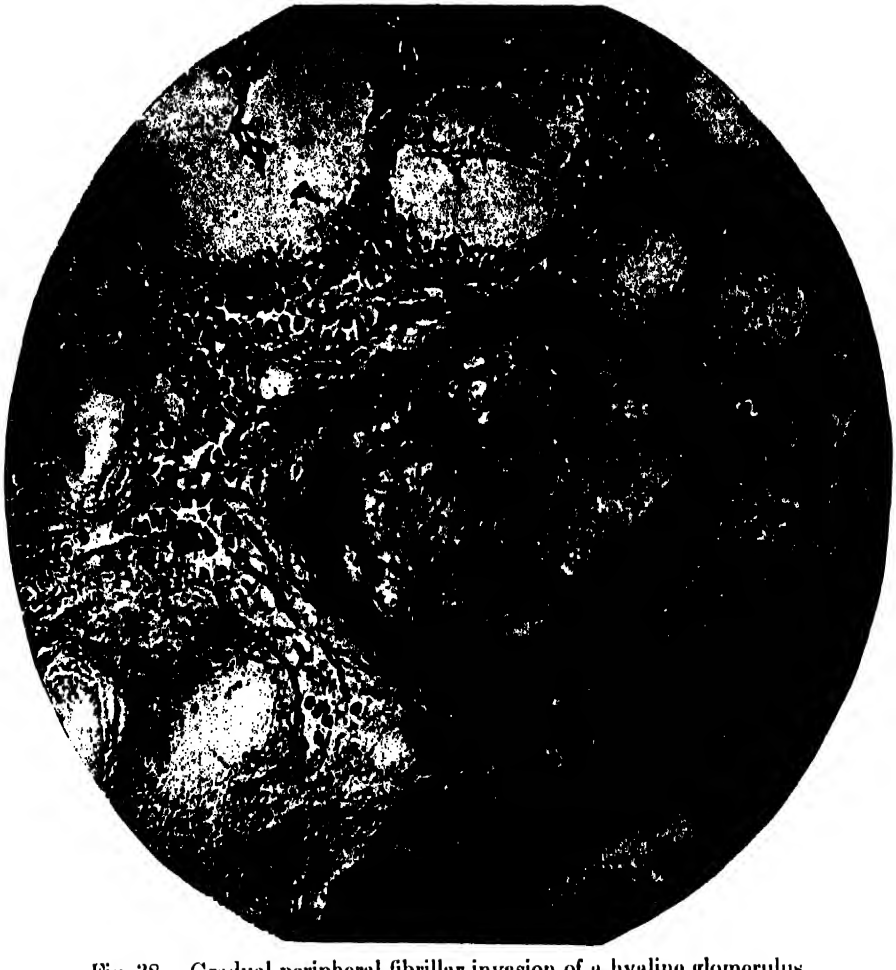


Fig. 38.—Gradual peripheral fibrillar invasion of a hyaline glomerulus.

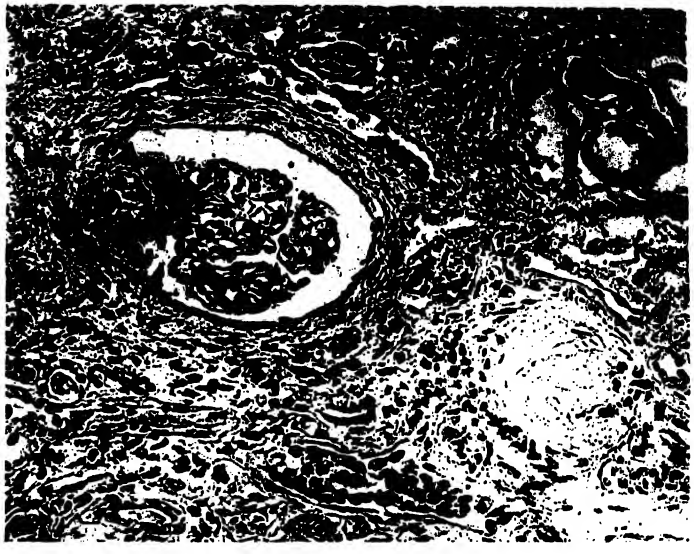


Fig. 39.—Capsular thickening with extension of lining cells before it and fibrous replacement from an attached point of the base of the tuft. Complete hyaline transformation of a glomerulus. Some of the tubules filled with newly formed cells. × 220.

Fig. 40.—Advanced and invading fibrous capsular thickening of a glomerulus. × 220.

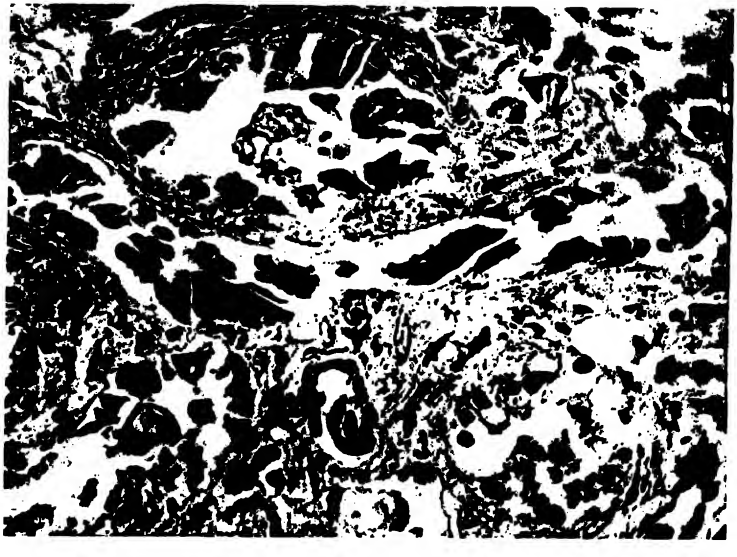


Fig. 41.—New cylindrical epithelium in tubules in productive nephritis.

exudate to a part of the capsule, which is usually close to the entrance and exit of the vessels, although it may occur in other parts of the capsule as well. Then it gives rise very soon to a fibroblastic proliferation of the connective tissue at the periphery of the capsule. But this is not only confined to the periglomerular tissue, which gradually thickens by the concentric deposit of fibrous tissue layers, but it invades the adherent tuft, and, gradually growing into it, replaces this by slowly maturing fibrous connective tissue. As an end-result the glomerulus has again been obliterated. It is interesting to note that this fibrous invasion and replacement of the glomerulus take place from the spot of adhesion to the capsule (Fig. 33). The connective tissue in the glomerulus, however, very soon suffers from the same nutritive disturbances that the obliterated tuft experienced, and, therefore, becomes gradually transformed into homogeneous material which, by fusion with the remaining tuft structures, gives to the whole glomerulus a characteristic hyaline appearance. Early in the process bands of connective tissue can be seen to grow into and separate hyaline or amyloid masses in glomeruli. This hyaline material still encloses cellular and particularly nuclear remnants. Later even these disappear, and there remains a dead-looking, non-functionating globule, surrounded by somewhat better preserved, usually loose and stretched, connective tissue. This capsular connective-tissue type of glomerular replacement has lately been particularly emphasized by Herxheimer[26] (Figs. 33, 34, 35, 36, 37). All types of fibrous glomerular replacements are associated with concentric periglomerular connective-tissue thickening. This is rich in elastic fibers.

We see that in the hyaline transformation of glomeruli all the component structures are involved, capsular epithelial, capillary endothelial, capsular fibrous connective tissue, assisted by

any exudate which may be present. The resulting hyaline bodies are of different composition. This is well illustrated by van Gieson's stain, which gives to the connective-tissue hyaline a distinct red, to the others a yellow color. According to Herxheimer, the yellow glomerular hyaline undergoes gradual resorption, while the red connective-tissue hyaline is more resistant. A late result is calcareous infiltration of the glomeruli—in my experience not a very frequent process. Baum has drawn attention to the fact that many of these calcareous small nodules are really calcified cysts, of which I shall speak later.

Coincident with all these changes, which, as you appreciate, are diffusely and very unevenly distributed throughout the kidney, go necessarily marked alterations in the size of the glomeruli. The best preserved glomeruli very soon undergo functional compensatory hypertrophy, the tuft enlarges to not only fill the capsular space, but to actually stretch it, and, therefore, enlarges the whole secreting apparatus. Unfortunately for the individual, such glomeruli are later apt to be overtaken by the same fate as the others. The atrophying and degenerating glomeruli, on the other hand, show much diminution in size, and the final hyaline remnants are usually smaller than the healthy glomerulus.

Now, the tubules also present gradually a very varied picture. As their epithelium undergoes different states of degeneration and desquamation, they enlarge, and become filled with cells and cellular débris, leukocytes, red blood-cells, and blood-pigment. All these may fuse, as we saw, into cellular, hyaline, or waxy casts. Fatty casts, of course, become frequent. Gradually these masses are pushed along, stagnating permanently or for a time on their downward way. This stagnation is aided by inflammatory obliteration of lymphatics. Proliferation of the epithelium is here also a prominent feature, and of the same

types which we met before, *i. e.*, inflammatory and regenerative. Inflammatory hyperplasia of epithelium occurs most abundantly in the loops, undoubtedly because the stagnation of necrotic masses irritates and demands phagocytic activity. In the convoluted tubules it usually remains confined to the tubular wall, and leads to many multinuclear, large, irregular cells, with, not infrequently, fusion and overgrowth to multinuclear giant-cells (Fig. 6). This proliferation may occur by mitosis, but according to my observations by far most frequently by amitotic division, and I would put this latter down as the rule for the multiplication of renal epithelium. In clear, or at least relatively clear, tubules the epithelium regenerates, but in an unusual manner. This newly formed epithelium, particularly well observed in the convoluted tubules, is frequently not of the normal, high, distinctly striated, granular, and protruding type, but of a low, smooth protoplasmic, in places syncytial, in others endothelial-like formation. The lumen of such tubules appears, therefore, much larger than in the normal kidney. Again, in some tubules the epithelium becomes high, narrow, and distinctly cylindrical (Figs. 28 and 41).

This newly formed epithelium is of great interest and importance, for the questions of the cause of this atypical formation and its function immediately present themselves. That glandular cells, when their environment changes, also change their type, is not a new or isolated occurrence here, but it is well known that in the sclerotic lungs, for instance, the alveoli become tubular, and their lining epithelium cuboidal; the same conditions prevail in the sclerotic, productive inflammations of the liver, and Milne[27] has shown that the so-called newly formed bile-ducts in the cirrhosis of the liver represent in reality old bile-capillaries, which, under the influence of the new environment, have changed their cell type. The same conditions prevail in the kidney, and

the influence of so many and variable conditions which, you appreciate, enter into this new environment, accounts in no small degree for the many atypical cell forms which we observe during the inflammatory hyperplasia. Ultimately, when conditions become more settled, a generally uniform, although morphologically different, regenerated epithelium forms as the result of more permanent, but changed, environment.

Of great practical interest is, of course, the associated functional change that must go hand in hand with such a morphological transformation. About this we know very little, but it seems as if certain complicated and obscure functional changes, which are always observed late in these nephrites, might possibly be traced, not only to the inflammatory involvement and anatomical rearrangement of the parts, but also to the loss of normal and the production of entirely new, secreting cell types.*

I shall refer to these matters again in the discussion of the so-called contracted, or interstitial, better termed, productive, nephritis, where these morphological and functional changes are most prominent and characteristic. Considerable variations in size of the tubules occur. Some are very much larger and dilated, either as the result of functional hypertrophy, or as the result of stoppage of cellular masses with stagnation of fluid above. Others again appear collapsed, and atrophy for reasons which we will presently discuss. This leads directly to the question of the result of such changes in glomeruli and tubules upon the kidney substance. Glomerulus and tubule are, as you appreciated, a unit from the anatomical and physiological standpoints. A permanent injury to one will necessarily involve the other. So it happens that the tubule whose glomerulus has been lost in either of the ways just described will collapse, atrophy, and ulti-

*This has been demonstrated in this institute for some time, and recently F. Müller (*l. c.*) has drawn attention to a similar observation. But it is really not at all infrequent, more so the rule.

mately be lost. On the other hand, a long-continued blocking of the tubule in any portion of it, and particularly frequent in the region of the loops, either by cellular masses, detritus, and especially by firmly attached casts, will soon lead all the structure above the point of occlusion to the same fate. While this has long been recognized as a factor in the loss of kidney structure in these lesions, it has recently been particularly emphasized by Ponfick[28] as an important cause for the waste of parenchyma. Indeed, Ponfick goes so far as to hold that much of the glomerular atrophy and loss must be attributed to a blocking of the tubules at a considerable distance below their origin. There can be no question that both of these mechanical factors are largely responsible for the gradual but progressive loss of substance, but they are much aided in it by the results of the inflammatory condition in the intertubular substance, which, by obliteration of lymphatics and capillaries, seriously interferes with the nutrition of the parts. These I will consider in a moment. But before doing so, it must be appreciated that, as a result of this irregular loss of substance, the kidney now begins to show areas of collapsed parenchyma, between better preserved and even swollen parts. The surface becomes, therefore, progressively slightly irregular, puckered, and this appears primarily and more prominently in the cortex. At this point the capsule still peels rather easily. However, this loss leads now to certain other changes, which alter still more the appearance and anatomy of the organ. They take their origin and pursue their development particularly in the intertubular tissue, and spread in a streaky and later diffuse fashion throughout the whole organ. We must, therefore, proceed now to consider the fate of this intertubular tissue from the time we left it in the process of degeneration and exudation. The fact that lymphatics and tissue spaces are here not cleared, but continue to be

blocked with fatty and cellular masses, while the inflammatory œdema continues, leads very soon to loss of these cellular elements, followed by a proliferation of endothelial cells within these channels and the appearance of lymphocytic (polyblastic, leukocytoid) and fibroblastic cells without. The cells thus produced are partly phagocytic and partly reconstructive; that is, a certain number aid in clearing the path for the development of fibroblastic cells. While this is primarily confined to the intertubular substance, and local, it soon assumes greater dimensions in all areas where adjoining tubules and glomeruli are wasting and atrophied. It stands to reason that this thickening and obliteration of the channels of nutrition and reabsorption must also interfere with the tubules and glomeruli, so that, in my opinion, these two changes interact and go hand in hand.

Now, as the fibroblastic cells mature, the intertubular connective tissue becomes less cellular, but thicker, and, by replacement of atrophied parenchyma, bands of connective tissue develop leading to more or less firmly contracting scars. By growth on the surface, the capsule becomes now irregularly adherent, so that it can be removed only with great difficulty, and usually takes some of the parenchyma with it. As these changes are most pronounced in the cortex, this suffers the most. It becomes very irregular, granular, cicatrices divide better preserved areas, and the normal markings have almost entirely disappeared, giving way to a bizarre arrangement and mottled appearance which varies much, and depends largely upon the condition of the vascular apparatus (Fig. 42).

Occasionally, but not frequently, the connective-tissue formation is very diffuse, without formation of thick, contracting scars; the surface therefore remains smooth, although the kidney shrinks. Both types are now recognized under the name of secondary contracted kidney.

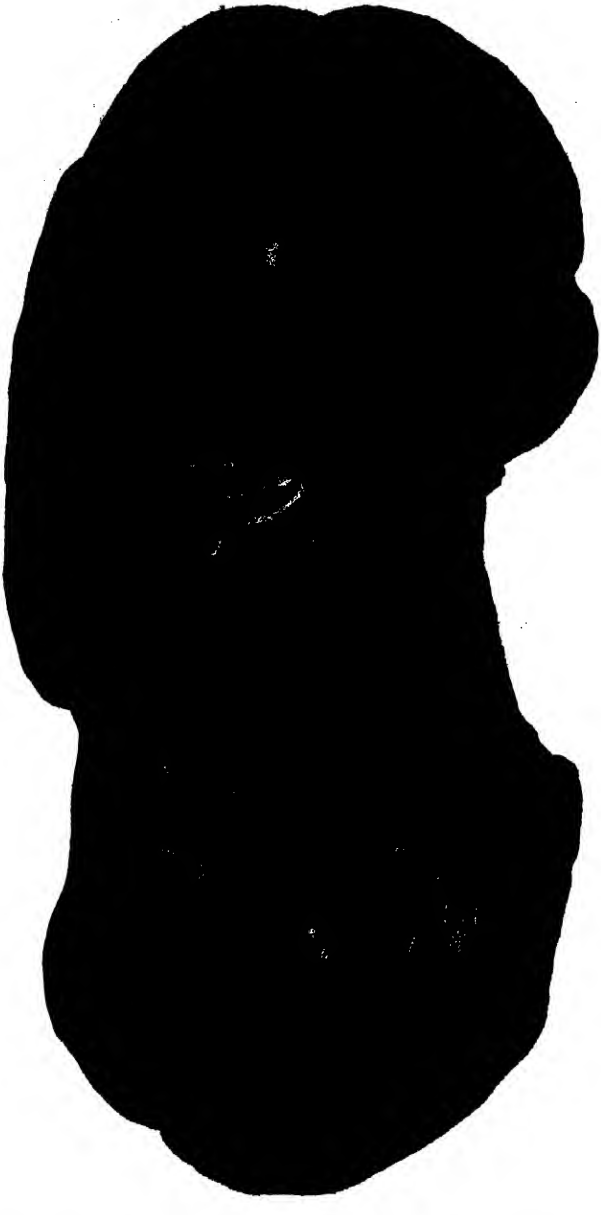


Fig. 42.—Nephritis degenerativa productiva, with an old healed infarct scar. A small fibroma in one of the medullary pyramids, weight 200 gms. (From a woman, fifty-three years old.) Generally swollen, but uneven and scarred surface, with collapse of renal substance and irregular fibrous tissue growth affecting the cortex very generally. On section, the parenchyma grayish, in places yellowish (fatty), glomerular rows obliterated or distorted, with formation of prominent compensatory vascular channels. A large piece of cortex lost as the result of a healed infarct, at its base a cyst. This kidney also showed evidences of a superadded venous congestion. Patient had a terminal fibrinous pericarditis.

As the condition of the vascular apparatus is of much consequence in the fate and appearance of such a kidney, we must now pay some attention to it. The vascularity of the kidney during the process of such a nephritis may be influenced in two ways: first and directly, by inflammatory changes; second and indirectly, by changes in the general circulation, which result from the effects of the nephritic lesions on the individual. We have seen before how in certain inflammatory lesions the affinity of the toxic excitant is particularly found and accentuated in the blood-vessels: abundant diapedesis of red blood-cells occur, hemorrhages and even extensive hemorrhagic extravasations. As a consequence, the kidney reddens, either diffusely or shows hemorrhagic dots and streaks, corresponding to hemorrhagic extravasations into the glomeruli and tubules. In others, again, the degenerative lesions, fatty metamorphosis, seem to emphasize that there the irritant effects a primary and greater injury of the fixed tissue-cells. In these cases the organ appears pale and yellow. Finally an œdematous imbibition in some forms, particularly those associated with general œdema, may give to the kidney an almost colorless, but moist, appearance. The kidney, therefore, shows here, as in other nephrites, the evidences which point toward one or the other inflammatory attributes, or both may become combined to about an equal degree. In addition, the vascularity must be influenced by the inflammatory anatomical changes in the architecture of the kidney. Weigert went so far as to hold that the quantitative differences in the blood-supply and inflammatory engorgement of the vessels accounted fully for the different appearances of these various forms of nephrites, and did not recognize them as independent lesions. Other investigators have endeavored to establish a definite hemorrhagic nephritis, distinct from the so-called large pale kidney. That there is no essential difference between these

various types was illustrated very forcibly to me only recently, when I found a typical large hemorrhagic kidney on the left side, and a similarly typical large pale kidney on the right side, of a young girl who died of a slowly progressing nephritis. It appeared to the unknowing as if these two perfect examples came from different individuals.

It has been claimed by some: Edebohls and his followers, who advise decapsulation of the kidney in nephritis, that with the attachment of the capsule to the parenchyma collateral circulation with the surrounding structures may thus be established, but extensive experimental observations of Thelemann, von Cott, and Herxheimer and Hall,[20] and others, have shown conclusively that this does not take place, and after decapsulation a new, much thicker capsule is soon formed.

Sooner or later the kidney begins to experience the effect of the nephritic process on the whole circulation. I will not discuss here these effects on the heart and vessels, which belong to the last chapter of these lectures, but it is particularly to the complicating pictures which venous stasis produces in such late nephritis that I wish to call your attention.

Venous stasis in the kidneys as the result of a general decline in the circulation in nephritis may occur rather early in the lesion, before secondary atrophy and contraction have taken place, or late, after this has much advanced. In either case it is apt to considerably modify the process, and to lead to very complicated anatomical and clinical pictures. If the circulation becomes impaired before much of the kidney substance has been lost, the venous engorgement may prevent at least a marked contraction of the organ altogether, and is sometimes responsible, I believe, for a remarkable good gross preservation in the size of the kidney. The distribution of the blood-vessels accounts for the fact that the stasis appears first and is best marked at the

junction of medulla and cortex. Therefore, the line of demarcation between both becomes more prominent. Later, the medulla shows accentuation of its vessels, which have usually been much better preserved than those of the cortex, and, finally, the remaining channels in the cortex also become more prominent. But as these, as well as the glomeruli, have largely been lost in the inflammatory process, this is relatively less conspicuous. While, then, the kidney as a whole feels fuller, is engorged with blood, and denser, this occurs relatively at the expense of the cortex, being at the same time most prominent in the medulla. After venous stasis has existed for some time, it leads to œdema and hemorrhages into tubules.

In the progress of the lesion, if the individual does not succumb, which is usual, it is difficult to separate the effects of the stasis from those of the nephritis, as the quantitative and qualitative conditions become well and completely interwoven. Where the blood stagnation is marked and patchy extravasations occur, hæmolysis with setting free of blood coloring-matter and precipitation of granular pigment in such affected areas takes place. These superadded nutritive disturbances are an additional cause for patchy atrophy and collapse of certain parts, while others show compensatory stretching and fullness.

Clinically such advanced cases present great diagnostic obstacles, on account of the necessarily complicated functions. These cases are frequently very difficult to separate from long-continued simple stasis with failing heart, and the question of determining whether we have primarily a heart lesion with progressive venous stasis or primarily a nephritic lesion, which has led to circulatory disturbances and a secondary venous congestion, may be impossible to solve.* In hospitals which, like ours

*Professor Senator has told me that Traube used to pay particular attention to the color of the urine in such cases. In venous stasis complicating a nephritis the color remains pale in spite of lessened quantity.

(City Hospital, New York), receive a large number of these advanced cases, some almost moribund on arrival, they are, as you know, more or less naïvely classed as cardiorenal, which leaves the ultimate diagnosis to the pathologist. While this is not a very scientific or even definite diagnosis, I believe that such clinical diagnoses, although practically confessing ignorance, are better, for the sake of reliable statistics, than an elaborate antemortem anatomical diagnosis, which cannot be controlled by autopsy.

Now, on the other hand, venous stasis may not occur until late in the disease, and after secondary contraction has well advanced. While it follows, then, the general course I indicated, it necessarily appears much more irregular, particularly in the cortex, where many of the vascular paths have been either entirely lost or obliterated, and distorted. The kidney in all these cases loses much of its pale or yellowish color, and assumes a darker, cyanotic appearance. The superficial veins appear prominent. Here, as in ordinary stasis, cyanosis is accentuated in the medulla, and must not be confounded with hemorrhagic inflammation or inflammatory exacerbation: these are always more prominent in the cortex, and never lead to dilatation of the larger veins. They may, however, combine.

Lastly, to sketch the functional evidences which correspond to the morphological changes studied in this lecture: When you consider the multitude of interacting, constantly varying processes which are here involved, and the time over which these extend, with the possible complications, I think you will appreciate that similar and sometimes very complex and perplexing functional corrolaries will go with them.

As long as the processes of exudation and degeneration control the field, the amount of urine is diminished, although on account of the less brusque process, and compensatory action of

preserved glomeruli, it is somewhat larger in quantity than in the severe degenerative and exudative nephritis investigated in our first lecture (usually about 500 c.c.). For the same reason blood is not apt to be present in large amounts, and the urine appears therefore lighter in color, particularly as the normal coloring-matter of the urine is not secreted in the usual quantity. Serum-albumin and nucleo-albumin are present in considerable quantities, the former from 0.5 to 2 per cent., but only rarely more, and the higher percentages reported refer to those of volume. The urine is very rich in morphotic elements, and as the fatty degenerative feature becomes now marked, its evidences are abundant in the microscopic examination of the sediment. Fatty cells, fatty casts, free fat, and detritus, above all others, give the lesion a characteristic stamp as fatty nephritis. Where, in addition, hemorrhages occur, the blood appears in the urine, but not with the same constancy or abundance as in the more active lesions previously considered. As the process proceeds and the exudative features regress gradually to the background, which allows the field to be somewhat cleared and superseded by the atrophy and loss of the tissue with productive cicatrizing changes, the functions show corresponding changes. The amount of urine rises; it becomes paler and clearer. The specific gravity, on the other hand, is lowered, because the excretion of normal solids is not improved; the amount of serum-albumin and morphotic elements is diminished. Finally, when the process of secondary contraction is well under way, with relatively free paths, and the glomeruli largely obliterated and non-functionating, the evidences of the previous, or still existing, exudation are usually slight, but the urine surprisingly large in quantity and much clearer, almost watery, and of low specific gravity. This increase in amount of urine is usually coincident with a decided diminution in the general œdema, which, as you know,

is most always very marked during the early stages of this nephritis, and which we will more fully discuss in the next lecture. Albumin and morphotic elements diminish correspondingly. One must be careful to not regard this frequently abrupt and perplexing deceitful change, sometimes associated with a feeling of relief on the part of the patient, as one for the better. If you have carefully followed what I presented to you here to-day, you will bring these evidences in proper relation to the morphological changes incident to the progress of the disease, and admit no repair or improvement. In reality, we are dealing with a further advance in the loss of renal substances and sufficiency, another step on the downward road to the fatal termination. The last is frequently hastened by an exacerbation of the exudative and degenerative processes. Then the kidney presents again, as much as it is able under the changed conditions, these various anatomical and functional features. But it is possible that an individual may survive one or even more of these exacerbations.

On the other hand, when venous stasis becomes manifest, this is responsible for other superadded functional derangements.

Here also the urine diminishes again, but, contrary to the inflammatory exacerbations, does not lead to a greater albuminuria than formerly existed or to an increase in morphotic elements. Later a relatively small admixture of blood-cells becomes evident, but the color of the urine remains pale. Recognition and relation of this complication to the nephritic process may at times be difficult.

I cannot leave this discussion without at least mentioning certain related kidney changes which develop late in primary chronic venous congestion, and not as the result of nephritic lesions. You understand that frequently in diseases of the heart with gradual failing compensation, long-continued venous congestion will

occur, without any previous inflammation of that organ. Here all the veins become enormously and progressively engorged, first in the medulla, later in the cortex, until the engorgement even affects glomeruli and arterial vessels. The kidney enlarges, becomes extremely rich in blood, and its markings very prominent. Later, it assumes a more diffuse, cyanotic appearance. As the result of the mechanical pressure and interference with nutrition, serum will transude into the intertubular tissue. The kidney appears, therefore, in later stages, œdematous, and the interstitial tissue stretched, homogeneous, and fibrillated, especially in the medulla, while the tubules are relatively compressed. Later, blood extravasations occur into tubules, and secondary hæmolytic changes, with setting free of blood-pigment. The latter is particularly well shown in the glomeruli. Now, as the result of these largely, and primarily quantitative, changes, atrophy of glomeruli and tubular portions occurs, followed by collapse of kidney substance. In such areas cellular lymphocytic and fibroblastic masses may accumulate, leading to more or less prominent fibrous tissue growth. As a result, the kidney shrinks and contracts in places, and the surface appears necessarily more coarsely granular. When tubules have become cut off, cyst formation may take place under such conditions, particularly in the medulla. This kidney has been described as cyanotic induration, or cyanotic contracted kidney, and is, strictly speaking, not of an inflammatory type. It differs from the inflammatory lesions in the evidences of its extreme cyanosis, associated with general œdematous imbibition and massive prominence of the larger vascular channels. This state of affairs never reaches equal uniformity of distribution or the same dimensions in a stasis which is engrafted upon a previous nephritic lesion. The contraction of the organ in the cyanotic induration, on the other hand, does not ever acquire the proportions often

seen in the inflammatory processes, but the kidney, although coarsely granular, remains large, and the medullary portion particularly prominent, bulbing, and the cortex never excessively scarred. Microscopically characteristic are absence of marked degenerations, or evidences of old or recent cellular exudation. This is particularly well shown in the glomeruli. These, although immensely engorged with blood and some escape of serum into the capsular space, with occasional adhesion of the tuft to the same, do not present any features of active exudation, nor that general, cicatricial, and hyaline replacement which formed so prominent a feature of the inflammatory conditions. Dense periglomerular cellular infiltrations and fibrous tissue growth are also absent, but whenever this forms, it grows less abundantly, carries many engorged blood-channels and tubules with old blood-pigment, and throughout has a characteristic, pale, œdematous appearance, with considerable fibrillar stretching. Schmaus and Horn[30] have pointed out that all vessels, arteries, and veins are here enormously thickened.

The consideration of the secondary contracted kidney has already ushered in certain new problems, which I have either only touched upon, or held over for the consideration of the productive types of nephritis, to which we will next devote our attention.

FIFTH LECTURE*

Productive Nephritis. Changes in Other Viscera. Œdema

Gentlemen:

I turn to-day to the last chapter of nephritis, to the consideration of that type I grouped as productive nephritis, and which is usually spoken of as chronic interstitial nephritis. I believe that its appearance, at least grossly, is familiar to you. We understand by it an extreme atrophy of the parenchyma, with an abundant increase in fibrous tissue. Such a kidney is very small: the smallest kidneys on record are of that type. The surface is extremely irregular in the uncomplicated pure cases, finely granular, with delicate cicatricial contractions. It is either reddish in color or pale, sometimes yellowish pale. On section it is perfectly evident that there is a marked diminution and loss of kidney substance, particularly in the cortex most of it may have completely disappeared. In cases complicated with arteriosclerotic infarctions deep cicatrices form and interchange with the finer granulations. The normal markings are usually entirely obliterated. Glomeruli and glomerular rows cannot often be made out at all. The glomeruli appear more frequently on the cut surface, in the form of small, point-like, pale hyaline elevations. On the other hand, in places, unusually dilated, irregular vascular channels run through the cortex. That, as you will appreciate in a moment, is produced by the peculiar circulatory modifications which prevail in this kidney. The intervening tubular parenchyma, depending on the vascular

* Delivered on February 22, 1909.

condition, is either quite pale or pinkish. Smaller and larger cysts, sometimes acquiring considerable dimensions, are also commonly distributed through the cortex, occasionally at the junction of medulla and cortex, rarely deeper in the pyramids. As a rule, this line of demarcation between cortex and medulla is poorly defined, except in cases where stasis has complicated, when the vessels of the pyramids are unusually prominent, and radiate well into the cortical remnants. Sometimes calcium or urate deposits may here be seen. When inflammatory exacerbations have supervened, or hastened the final termination, the whole kidney appears more diffusely reddened or mottled. In cases of far-advanced contraction the pelvis is relatively very large and very fatty. The fat extends well upward between the atrophied pyramids. Very prominent are the thickened arteries. This thickening may involve only the smaller ones, which, on section, stand out prominent and gaping, or it may go so far as to affect the renal artery (Fig. 43).

Two questions present themselves to us from the start: What is the relation of this form of nephritis to the changes previously discussed, particularly the so-called secondary contracted kidney? and, secondly, What is the relation of that extreme parenchymatous loss to the abundant fibrous tissue proliferation?

With regard to the first question, you recall that Bright, who took a uniform view of the whole nephritic process, regarded the contracted kidney as the last stage of the previous two, and a similar view was entertained by many subsequent investigators, notably Henle, Reinhardt, Frerichs, and especially Weigert. On the other hand, Christison, while acknowledging this to some extent, was the first to doubt that all these various lesions were stages of one morbid process. This gained much support in England in the works of Johnson, Toynbee, Simon, and Busk,

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Fig. 43.—Nephritis productiva. Kidney small, weight 56 gms., from a woman forty-six years old. Surface flattened and finely granular, pale. Cortex uniformly and markedly narrowed, so that the better preserved medulla appears drawn to the surface. Normal markings lost. Whitish areas (mature fibrous tissue) interchange with reddish (vascular granulation tissue) or yellowish-red parts. All vessels distinctly thickened, around them frequently white fibrous patches. Pelvis relatively large. Here also was a terminal fibrinous pericarditis.

with which we became familiar in the first lecture, until finally Samuel Wilks and Grainger Stewart regarded the large white and the small granular kidneys as independent affections, and Gull and Sutton even spoke of "arteriocapillary fibrosis" as the cause of contracted kidney. Similar, although not so radical, were the ideas of Bartels in Germany, who definitely separated the so-called primary interstitial nephritis from the others; in this he was followed by Ziegler and his pupils. Senator, you remember, took a somewhat reconciling view, inasmuch as he holds that all these various forms may be definitely related, or, on the other hand, may develop independently, and also result as the consequence of primary arterial changes. Inflammatory exacerbation in them may occur at all times. Finally, the tendency on the part of some modern pathologists and clinicians Marchand, Löhlein, Müller seems to be again toward the older uniform view of Bright. It has been pointed out by them that it is extremely difficult, if possible at all, to separate the secondary contracted kidney from the so-called primary interstitial nephritis, and that, in all probability, many of the latter are the results of previous exudative inflammatory conditions, which have remained latent or progressed exceedingly slowly. It has been claimed by some that the secondary contracted kidney is an anæmic one, in which, even after much loss of substance, the degenerative features still predominate, and that, on the other hand, the primary productive nephritis appears as the typical small red kidney.[1] Against this, however, it has been urged that the small red contracted kidney represents only a later stage of the large hemorrhagic degenerative nephritis,[2] which has a much greater tendency to contract, on account of better nutrition and, therefore, leads to abundant connective-tissue formation. My own experience in the matter has led me to believe that there is no essential anatomical difference in any of the changes

which occur in this type of productive nephritis from those which we observed in the other forms and which we have discussed in detail. On the other hand, it cannot be denied that there exists a nephritis the development of which differs in certain points from those we have considered: Inflammatory features are neither so intense nor so general and diffusely distributed from the start as in the types of nephritis previously discussed. The process presents itself as a gradually advancing, patchy inflammation, leading to a progressive loss of circumscribed areas of kidney substance, while other parts are preserved and their functions continued and compensated. Gradually, by changed anatomical conditions, an unusually complicated organ is thus formed, whose functions show marked abnormalities. On account of this slow progress and a gradual adaptation of the organism to these conditions, it is compatible with a longer period of life. Such a kidney, however, is easily vulnerable, and may experience at any time an active and diffuse inflammatory exacerbation, placing it in the category of the types previously studied.

I am, therefore, of the opinion that anatomically no particular feature differentiates any of the contracted kidneys one from the other, but believe that the mode of origin and development may differ. It may result, first, from a diffuse inflammation (the so-called secondary contracted kidney), or, secondly, very insidiously, as the consequence of slowly progressive circumscribed inflammatory foci, which eliminate kidney substance very slowly, and, therefore, normal functionating parenchyma is retained for a considerable time. This distinction is in reality a purely relative one, and, taken with the time, accounts for certain modifications in one more frequently than in the other. In the end the result is the same, but may be considerably hastened by inflammatory exacerbations. From this standpoint an

essential difference between primary and secondary contracted kidneys does not exist, except in the localization and progress of the disease, and both are really secondary to previous degeneration and exudation, in one with a latent, in the other with an active, course.

The terms primary and secondary, contracted and interstitial nephritis are misleading, therefore, and had better be dropped altogether. Anatomically, we should speak of productive nephritis, then, when the exudative and degenerative attributes are less prominent and, on the other hand, the formation of connective tissue very abundant. It is evident, therefore, that the causes of productive nephritis are very numerous. It may either result from a previous diffuse exudative degenerative nephritis which has undergone remission and cleared in certain areas, so that conditions for a patchy progress of the disease are thus created; or it develops very insidiously, usually quite unknown to the individual, until it reaches an advanced degree, and, as the consequence of long-continued intoxications—lead-poisoning, etc., gout, and probably metabolic autointoxications. These may lead directly to patchy, irregular injury and corresponding inflammatory foci, with eventual loss of kidney substance.

In the description of this productive nephritis we may safely disregard all the various changes which presented themselves to us before, and devote our attention mainly to those characteristic features which appear especially accentuated in it.

From these considerations it becomes intelligible that the kidney of a productive nephritis offers the greatest variety of pictures. It represents really a combination of all the inflammatory features which we previously discussed. Far-advanced fibrous areas with hyaline, contracted glomeruli, lost or distorted tubules, may change abruptly to better preserved and

even healthy kidney parenchyma in the state of compensatory hypertrophy. This, again, adjoins patches of kidney substance which are the seat of recent inflammatory degenerative and exudative foci. The latter are particularly prominent in the intertubular tissue, and consist of lymphocytic and polyblastic cells, which, accompanied by fibroblastic proliferation, soon lead to considerable stretching and thickening of the intertubular tissue, and the formation of waxy, mature, fibrous connective tissue. Similar lesions prevail around and within the glomeruli, and as we have become fully acquainted with them, I shall not discuss them here again. On account of the slow and patchy progress in these changes, and the compensatory possibilities, the nutrition of the organ is, as a rule, in much better state than in the cases of brusque and general nephritis, where inflammatory detritus and general inflammatory swelling seriously block the nutritive channels. As a consequence the production of new cells and fibrous tissue occurs here with much greater abundance and perfection than would be possible under these conditions.

These very slow developments are also responsible for a complete and permanent new arrangement of the components of the kidney. I consider this of the greatest importance, as it accounts in no small degree for some of the perplexing functional deviations which are very characteristic and constant. These anatomical changes manifest themselves in the parenchyma and in the vascularity of the kidney. Both are intimately connected.

In the tubules two changes occur: First, a complete regeneration of epithelium, of the type which we met before—low, smooth and syncytial, endothelial-like. On the other hand, it is not uncommon to observe the formation of high, cylindrical epithelium within old tubules. One or the other change is so general that we may safely say that the kidney gradually acquires an entirely foreign epithelium, being morphologically and undoubt-

edly functionally distinct, and different from its predecessor. It is most conspicuous in the convoluted tubules. Secondly, the tubules change their size, shape, and course. They become more tortuous, are frequently of an adenomatous type, giving rise, therefore, to a different glandular system from the normal uriniferous tubule.

Of greatest importance is the elimination of the glomeruli, as it necessitates and accomplishes an entire change in the circulation of the kidney. It has been shown by Thoma[3] that, where glomeruli become impermeable, circulation may be kept up by a direct union of afferent and efferent vessels, so that blood reaches the tubules direct, without circulation through the glomerulus. On the other hand, in places where complete loss of cortical substance has taken place, compensatory dilated channels form in the cortex; finally, when this becomes impossible by destruction of whole cortical capillary systems, medullary vessels are pressed into service. Under such conditions, the blood reaches the medulla directly, avoiding the cortex altogether. This is grossly well illustrated by the appearance of abnormal and enormously dilated vascular channels within the cortex and medulla.

You are now in a position to appreciate that in the well-developed cases of this type of nephritis we are dealing with kidneys which represent entirely reconstructed organs. The glomeruli have been eliminated, the tubules have not only changed their epithelium, but also their course, and the whole vascularity of the organ has been altered. No blood circulates through glomeruli, and much avoids the cortex altogether, to proceed directly to the medulla. As the consequence of these essential interferences with the structure of the kidney, far-reaching functional modifications necessarily develop, vastly different from anything ever observed under physiological conditions. You readily understand how difficult it will be to

explain the functions of such a radically changed organ on the hand of simple physiological experience.

But before sketching these pathological functions for you, we must consider some other morphological features of this nephritis.

Of great frequency are cysts. These occur, sometimes few, at other times in great number, so that the name of acquired cystic kidney has been given to such cases. The size of the cysts also varies greatly. From small, point-like prominences, they may grow to grape-sized, or even egg-sized, globular bodies, but never to the dimensions of the congenital cysts. The larger ones contain usually a thin, watery, clear fluid; in the smaller ones inspissated, yellowish or greenish material is not infrequently found. These latter may, as Baum[4] has shown, calcify. The origin of these cysts is twofold. In the first place, they represent parts of isolated uriniferous tubules, which, having been cut off by the sclerosing inflammation, undergo cystic dilatation. It is, therefore, held by some that the cyst fluid represents retained urine. But the different nature of the lining epithelium of such cysts, as well as the physical and chemical character of the fluid, makes a modified secretion probable. On the other hand, I observed a good many years ago—in 1895, while working in Würzburg—that some of these cysts are distinctly of glomerular origin. This can be directly observed in certain smaller ones, where location, size, and arrangement of the wall and lining epithelium stamp the cyst body as of glomerular derivation. Such cystic bodies frequently contain what I considered remnants of the glomerular tuft. I held the opinion that these cysts owed their origin either to a sclerosing inflammation or to a stagnation in the upper parts of the tubules. Baum, however, who has investigated that matter later, regards them as congenital, and as an incompletely developed glomerulus. But his arguments are not entirely convincing.

Of the greatest importance and interest are the vascular changes. The arterial changes in nephritis, like those occurring outside of it, have been a much-discussed subject, and even now there is no exact agreement as to their pathogenesis and relation to the nephritic process. We may, I believe, differentiate here between two types of arterial thickening which depend partly upon the local inflammatory changes and partly upon the results which outside influences produce in the arterial system of the kidney. Consequently we may differentiate between, first, an inflammatory thickening dependent upon the local long-continued productive inflammatory processes. This plays a part primarily in the adventitia of the vessels. Perivascular infiltrations combine with fibroblastic proliferations and lead to thickening of the adventitia. Frequently, however, the lesion progresses toward the lumen of the vessel, thereby adding an endarteritis fibrosa obliterans. The latter is particularly the case in the smaller vessels, and may possibly also be traced to a direct toxic action on the intima.

Second, the vessels may show a process of arteriosclerosis or atherosclerosis. The relationship of this to nephritis, particularly, has been a much-discussed matter.

We owe primarily to Jores,[6] and later to him with Prym,[7] an extensive study, not only into the histology of the lesion, but also into the gradual development of the arteriosclerotic process, and lately Fahr[8] has added a study with particular reference to the kidney. Jores—and this has been corroborated by others—distinguishes between two types of arteriosclerosis: First, hyperplasia of thick elastic lamellæ, which are derived from the internal elastic membrane. This is, in reality, a perfectly physiological process which may be traced from early childhood. This thick, elastic, internal membrane displays a great tendency to degeneration and fibrillar disintegration, associated with fatty

degeneration of the part. Jores regards these processes as the essential feature of the arteriosclerotic process. This in turn is followed by connective-tissue formation. Secondly, Jores describes, as a distinct process, a simple connective-tissue proliferation of the intima, the so-called endarteritis fibrosa. He looks upon the gradual formation of the elastic lamellæ as a compensatory process, one that is necessary for the maintenance of arterial elasticity. These views are opposed to those originally offered by Thoma,[9] and also Ewald[10] and Friedeman,[11] Rindfleisch, and others, who look upon the rise in blood-pressure as a cause of arteriosclerosis.

Corroboration and extension of Jores' views have recently been advanced by Fahr. He not only traced the same development of the process from early childhood to old age, but drew attention to the fact that in the heart appears early a fine elastic network, which during later life may take on considerable dimensions. Fahr brings this into analogy with the arteriosclerotic process. On the other hand, he, and also Roth,[12] emphasize the fact that the occurrence of arteriosclerosis in the kidney seems to bear no relation to the nephritic process. This is particularly corroborated in the nephrites of the young, when, in spite of high blood-pressure, little or no hyperplasia of the intima occurs. Again, this may be marked in cases when no productive nephritis can be demonstrated.

Based on his observations, Fahr concludes that arteriosclerosis of the renal arteries is an extremely frequent phenomenon. It may assume considerable dimensions without seriously interfering with the kidney structure. On the other hand, it may lead to conditions which in time produce extensive contractions of the organ. The opposite, however,—arteriosclerosis as results of a nephritis—plays only a very subordinate rôle. Fahr believes, therefore, with Marchand, that the arteriosclerosis

Fig. 44.—Marked vascular thickening and narrowing in senile and arteriosclerotic kidney. × 112.

of renal vessels is not the result of a nephritis nor of raised general blood-pressure, but the expression of the daily variations in blood-pressure in a vascular organ, to which every individual is more or less exposed, depending upon occupation, temperament, and mode of living. In other words, a wear and tear process.

I believe, however, that it cannot be denied that long-continued increased resistance in the kidney as the result of obliteration of normal vascular paths may be a factor in producing elastic thickening of renal vessels. This view was particularly advocated by Rindfleisch. A combination may, therefore, occur with the third vascular change, which may be observed in these kidneys, which consists in a hypertrophy of all the coats, particularly of the *media*. This has been emphasized by Friedeman,[13] who separated this lesion distinctly from the arteriosclerotic process, although, as you appreciate, it may lead to or combine with it, so that a sharp line of distinction cannot always be drawn. This process is characterized mainly by a hyperplasia of the muscle-fibers of the media, which distinguishes it from granulomatous arteritis, endarteritis, and arteriosclerosis. In them, you remember, there occurs essential loss of muscle tissue, with fibrous or elastic tissue replacement. Indeed, Adami looks upon this as the essential feature of arteriosclerosis. The arterial muscular hypertrophy, however, has been traced to the same causes which demand excessive muscular contraction elsewhere, and which, as we will see later, find marked expression in the hypertrophy of the heart. But here again the local conditions and gradual increasing impermeability of the vascular paths in the progress of a nephritis may also play a rôle.

Finally, the capillaries show inflammatory endothelial proliferation. This necessarily leads to thickening of their walls, and frequently they undergo hyaline transformation.

We see, therefore, that the thickening of the vessels which is observed during the progress of a nephritis originates either from conditions arising within or outside of the kidney, and that, as in the hypertrophy of the elastic tissue and the media, both factors may be active. But whatever may be their origin, they, in turn, are apt to very materially influence the progress of the lesion. This occurs particularly in the arteriosclerotic and the inflammatory endarterial changes. These are naturally followed by marked diminution in the caliber of the vessel, and, in time, lead to thrombosis and complete obliteration of the thus affected vascular channel (Fig. 44). The result of such an occlusion, however, has, particularly in larger vessels, a decidedly bad effect, as it is necessarily followed by infarction of the area supplied by that vessel. That part undergoes, therefore, necrosis, is entirely lost, and heals only with the formation of a deep, thick scar (Fig. 42). Almost all advanced cases of productive nephritis show these evidences of previous infarctions.

This leads directly to the consideration of the so-called arteriosclerotic and senile kidney, which is usually classified as the arteriosclerotic type of productive nephritis. I speak of it as sclerosis or atrophia renum, because its inflammatory nature appears very doubtful. It is the typical senile kidney, and on account of some similarity to the productive types of nephritis, has frequently been considered as identical with it. There are, nevertheless, certain features which justify its separation from the inflammatory productive nephrites.

As the name implies, this kidney appears during later life. No definite time for its development and occurrence can be given, any more than an exact answer to the question, When do people age? Indeed, the senile kidney is dependent upon the general process of aging of the whole individual, and more particularly upon the conditions of its circulatory apparatus. It is, therefore,

Fig. 45.—Atrophia senilis arteriosclerotica. Weight 50 gms. From a woman, seventy-four years old, who died of gangrene of gut due to arteriosclerotic thrombosis of arteria meseraica superior. Extreme loss of whole kidney substance, and thickening of renal artery. Idiopathic hydronephrosis extending to cystic dilatation of the medullary pyramids.

eminently a nutritive disturbance, into the production of which three factors enter: First, and paramount, the condition of the blood-vessels of the kidney; second, the condition of the general circulation; third, certain organic cellular changes incident to advanced life.

In our previous discussion about the arterial changes we learned that the vessels of the kidney are particularly exposed in an unusual degree to the wear and tear of life. Outside of the spleen, there is perhaps no other organ which is so constantly under marked variations of pressure, tension, and rapidity of blood-current. All the arteries in advanced life show evidences of strain in the form of the various processes collectively grouped under the term of arteriosclerosis or atherosclerosis, but for reasons just mentioned it reaches in the kidney more general and much greater dimensions. With Fahr and Marchand we may look upon renal arteriosclerosis as physiological for advanced life; so it happens that a characteristic, rather constant feature of the senile kidney, recognizable almost at first sight, is pronounced thickening and narrowing of its vessels.

The results of these, and possibly still other, interferences with the nutrition of the parts show themselves in parenchymatous atrophy of circumscribed areas of the kidney substance. The glomeruli and the connected tubules shrink, become hyaline, and thus the involved portion collapses. This loss of substance gives rise to the formation of slowly maturing granulation tissue, rich in engorged blood-vessels, usually taking origin around vessels; compensatory and sometimes considerable enlargement of the neighboring structures follows, unless they also have become involved in a similar fate. The process, which commences in small patches, may finally affect a considerable portion of the whole kidney substance. Remnants of tubules have become buried within the increased fibrous tissue as adenomatous loops or as

cystic papillary bodies. Small hyaline globules may be the only evidences of previous glomeruli. The kidney, as a whole, diminishes therefore in size and appears irregularly granular, and, depending upon its vascularity and the presence or absence of serous imbibition, which I will discuss in a moment, is either red or pale.

This state of affairs has almost always added to it stasis. The latter depends partly upon new circulatory conditions within the kidney, partly upon the gradual weakening of the general systemic senile circulation. The results of such a long-continued stasis are here similar to those which we met before, namely, dilatation of all vascular districts, including the newly formed capillaries within the fibrous tissue, further interference with the nutrition of the parts still intact, and a gradual serous imbibition of the tissues, particularly marked in the medullary portions.

The kidney, therefore, becomes œdematous. Its general appearance is hazy; the markings become disturbed and less distinct. It is for these reasons that kidneys in such a stage are frequently, but wrongly, spoken of as nephrites, and not infrequently such kidneys are regarded as an inflammatory exacerbation of contracted kidneys. But, as you see from the short description of its pathogenesis, it represents the late results of a long-continued venous congestion superadded on non-inflammatory nutritive disturbances.

But the picture may become still more complicated; for the arteriosclerotic process frequently leads to complete obstruction of the larger vessels, necessarily followed by infarctions. These infarcts, which occasionally are of considerable magnitude, heal with the formation of deeply retracting scars. It is herein that this kidney differs particularly from the pure types of productive nephritis, and it gives the organ a coarsely granular surface. It is the type of kidney which led Gull and Sutton to their views about the pathogenesis of nephritis.

Finally, I should mention that it must be considered doubtful whether all the atrophic changes observed in the senile kidneys—and that applies in general to all senile organs—only and absolutely depend upon the quantitative influence of arterial changes. No doubt, these are extremely important. There are, however, certain evidences, the discussion of which lies outside the scope of these lectures, which seem to indicate that senile atrophy of cells cannot be entirely ascribed to the changes within the circulatory apparatus, but include certain other qualities inherent to cell life. Indeed, we observe some senile kidneys without much arteriosclerotic coarse contraction, but a rather uniform, simple loss of secreting substance, the surface remaining smooth.

A characteristic feature of this type of kidney, and already mentioned in my second lecture on the theories of urinary secretions, is not only a relatively, but absolutely, large pelvis, which sometimes takes on such dimensions and appears so dilated that it may properly be spoken of as hydronephrosis. This hydronephrosis may be regarded as an idiopathic one, for the reason that it cannot be attributed to any coarse mechanical interference with the outflow of the urine, but appears to be due to a gradual decline in the elasticity of the contractile elements of the pelvis, and, possibly, of the ureter. In some of these pelves one observes distinctly a disintegration of the elastic structures, which appear either increased or markedly diminished. This point has considerable practical interest and bearing.

It is evident that senile kidney will, sooner or later during life, eliminate enough kidney substance to produce symptoms of renal insufficiency. Here pathological and clinical classifications have some difficulty in harmonizing, for a clinician will necessarily be satisfied to group such cases under the general category of nephritis, while the pathological anatomist can surely not be content with this.

We are now in a position to appreciate that not every granular, cicatricial, and atrophic kidney is a nephritis. It may result, as we saw before, from a long-continued venous cyanosis, and, as we find now, from nutritive disturbances incident to senile changes. Even the anatomical diagnosis may here not always be easy, and must be made with thorough appreciation of the factors which we have studied. But the decision of this point, particularly in relation to certain cases of hypertrophy of the heart, may become of the greatest clinical importance. Great difficulty may be offered in cases when such kidneys—as you can readily imagine—become the seat of superadded exudative and degenerative inflammatory conditions.

Let us return to the subject of productive nephritis. We have arrived at the second question which presented itself at the start of this chapter: What is the relation of the extreme parenchymatous loss to the abundant fibrous tissue proliferation?

Here we step once more on very disputed ground. You will recall from the first lecture that there are two entirely opposed views on that subject. It had been Weigert's idea—and in this he was essentially supported by Cohnheim and many others—that it was necessary to presuppose a parenchymatous injury in order to account for the fibrous tissue growth. He regarded this latter, therefore, as strictly compensatory. An entirely different view, however, was entertained by Bartels, who regarded the hyperplasia of interstitial tissue as the primary feature of the contracted kidney, and thus created the conception of the primary interstitial nephritis. In this he was actively supported by Nauwerck, who held that epithelial degeneration by no means always preceded the interstitial inflammatory changes.

Some, like Aschoff, separate entirely the connective-tissue formation from the inflammatory process, and, extending the

views of Weigert, look upon it as a process of repair. That group of investigators is therefore unwilling to speak of productive nephritis at all, but regards all the various lesions of proliferation and production of new tissue, much as Virchow did, as *consequences* of the inflammatory degenerative and exudative changes, which form no part of the inflammatory phenomena, but an evidence of healing. Aschoff discards the terms of chronic nephritis and productive nephritis, therefore, and speaks of nephropathia chronica inflammatoria. By this he means a long-continued disease of the kidney, originating on an inflammatory basis, but having reached stages of repair in various types of cicatrization. He recognizes this lesion in three stages: first, insufficiency; second, compensation; and third, decompensation.

Now, it is certainly true that many of the so-called "chronic interstitial inflammations," representing an increase of fibrous tissue at the expense of parenchyma, are not inflammatory at all. What is, for instance, frequently referred to as chronic interstitial myocarditis is generally scar formation as the result of infarctions. Similar illustrations may be found in other organs, and I have already insisted before you that in the cyanotic induration, and in the senile and arteriosclerotic kidney, we are dealing with nutritive disturbances which are absolutely unrelated to, and therefore to be separated from, the inflammatory conditions of that organ.

However, it is very doubtful whether the proliferation of cells and formation of new tissue, which is characteristic of certain inflammations and with which we are dealing in the question of productive inflammations, can properly be regarded only as evidences of repair, or as a pure healing process. There are some points which differentiate them from the previously mentioned fibrous growth which results from nutritive disturbances:

First: The changes in the interstitial tissue in inflammatory processes are characterized by an active participation of component parts of this tissue in the defense against the inflammatory irritant. The changes thus produced differ, therefore, quantitatively and qualitatively from those which occur during the process of repair. While, therefore, some of the features of repair are evident in the inflammatory interstitial changes, they have others so closely allied and acting with and modifying them, that one cannot well be separated from the other. Further, the close interchange between interstitial tissue, parenchyma, blood-vessels, and lymphatics lends, as we have learned, certain qualitative features to the inflammatory connective-tissue changes which go far beyond those found in reparative processes.

Second: The inflammatory interstitial proliferation always grows beyond the limits of repair. This important point had become evident even to Weigert, who therefore introduced the conception of hypercompensation, later used by Ehrlich in the elaboration of his side-chain theory. The process of repair, which is ushered in by nutritive tissue disturbances, remains distinctly limited. Into its formation enters, as far as can be seen, only the removal of the restraint of tissue tension. This once reëstablished, the proliferation ends and matures without affecting in the slightest degree the neighboring intact, or even weakened, tissue. The inflammatory interstitial proliferation, on the other hand, by virtue of its extensive and less restrained growth, by blocking the paths of nutrition and absorption, adds injury instead of repair. The causes for this must undoubtedly be sought in the inflammatory circulatory conditions and anatomical rearrangement of the parts, more complex changes of tissue tension than in simple repair, nutritive changes, and continuance of certain irritative influences.

Herein lies a very decided difference between pure reparative

and inflammatory tissue growth, and one which justifies us in upholding the conception of productive inflammation as distinct from processes of repair.

Now, an investigation into the problem of the relation of parenchymatous loss to the fibrous tissue formation is made extremely difficult by the complex nature of these changes, and by the fact that it is rare to obtain kidneys in such stages of incipient nephritis as will allow definite conclusions on that point.

It seems, however, as if somewhat intermediary and more flexible views would come nearer the truth than any one-sided and rigid idea: Certain forms of nephritis are associated from the start with progressive parenchymatous destruction. It appears that in these we cannot attribute the loss of parenchyma to primary proliferation of interstitial tissue, but that it is at least concomitant, and by its loss does not oppose an unrestrained connective-tissue hyperplasia. These cases would conform with Weigert's views. On the other hand, there exist types of nephritis which originate as primarily localized perivascular infiltrations. These localized areas, however, are rapidly followed, possibly by virtue of their existence, possibly by extension of the inflammatory irritant, or both, by nutritive disturbances of the involved parts. Parenchymatous destruction, therefore, ensues, and inaugurates the possibility of further extension of the inflammatory infiltrations and connective-tissue growth. With the second view we take, as you may see, a somewhat reconciling stand between extreme ideas.

Let me now touch upon some of the important functional characteristics of productive nephritis. One of the most interesting is the strange fact that throughout the course of this disease the urine quantity is very much increased. This increase, although not reaching such high figures as in diabetes, is nevertheless considerable, and, curiously enough, persists toward

the end. That is its most perplexing phenomenon. No matter whether we find at autopsy almost all the normal kidney substance destroyed, the quantitative excretion of the watery elements has remained high to exitus, unless circulatory disturbances or exacerbations complicate the terminal picture. We have no really satisfactory explanation for this phenomenon. It may, of course, be supposed that, particularly at the beginning of the disease, compensatory hyperfunction on the part of the preserved kidney portions occurs; but how does it keep up as the kidney substance wastes and is replaced by connective tissue? It is here particularly that we must look for other than purely physiological reasons. The kidney of an advanced productive nephritis is really not comparable to the normal organ.[14] Not only, as you remember, has there taken place far-reaching changes in the vascular supply and secreting channels, but the epithelium has, as you also recall, changed its type entirely. From a highly differentiated, specialized form, it has either become cylindrical or more frequently descended further to an endothelial, syncytial-like formation. These atypical forms of epithelium receive their blood, by elimination of most glomeruli, in unmodified, unconcentrated form. It is evident that this complete reorganization of parts must be followed by far-reaching effects. In the same way we may possibly account for the gradual lessened concentration of such urines, which, although frequently very high in the beginning, become lower in specific gravity, until toward the end the excretion of solids, in spite of an abundance of urine water, is far below any normal figure.

In other words, the late manifestations in the functional derangement of this type of nephritis seem to depend on new structural forms and arrangement, which are not comparable to the physiological. The organ is a new functionating unit.

If you have followed the morphological changes carefully, you will readily see that the urine in the pure types of productive nephritis must be poor in morphotic elements and serum-albumin. Destruction of kidney substance is very slow, certainly never intense, and wide-spread, rapid desquamation of epithelium, and the formation of much inflammatory detritus and active diffuse exudation being lacking. A moderate number of hyaline, occasional granular and fatty casts, often found only after considerable centrifuging, and occasional leukocytes, are therefore the only elements found. Serum-albumin exists only in traces, except where the lesion is complicated by amyloid degeneration.

Herewith we have finished our proposed work the consideration of the pathological anatomy and histology of Bright's disease as far as the kidneys themselves are concerned. From the mass of evidence and known facts, it has been my endeavor to select the most important, not presenting them as independent or incoherent descriptions and statements, but molding them into a plastic form which will allow you to form visual pictures and relations of the nephritic processes.

In conclusion, however, I must touch upon some features of nephritis which, although lying outside of the kidney, are really part of the general morphological consideration of the subject. First, changes in some other viscera; and, secondly, the question of œdema. These are so important and characteristic that we cannot well omit them. Of the changes in the viscera we immediately recognize those of the heart as the best known and very important. That any nephritis which extends over a longer period may become associated with a hypertrophy of the heart was known to Bright, and so overwhelming has been the evidence since his first observations, that this is one of the best accepted complications of nephritis. While the carefully tabu-

lated observations of Bamberger and Traube and general experience emphasized the preponderance of the hypertrophy of the left ventricle, it is really only very recently that indisputable evidence has been furnished about the manner under which the heart hypertrophies in nephritis. By careful weighing, according to W. Müller's method, Romberg, Hasenfeld, and Hirsch have demonstrated that in 82 per cent. of their cases all cavities of the heart, auricles and ventricles, show hypertrophy of their walls. The left ventricle, however, presents this most markedly. In 14 per cent only the left ventricle was hypertrophied.[15] Hirsch demonstrated that the hypertrophy of auricles and the right ventricle follows that of the left ventricle, and Pässler that the right side only hypertrophies when the left side becomes insufficient.

These figures are accepted by Krehl as perfectly conclusive. They are, however, as now all pathologists and clinicians know, open to some variations.

In the first place, it is well settled that hypertrophy of the heart occurs only in those cases which are associated with an appreciable rise in blood-pressure. It is, therefore, not absolutely dependent upon or associated with any particular kind of nephritis. While it is most constant in the brusque exudative types, particularly those with marked vascular injury, as in scarlet fever, and in the productive forms, it may, nevertheless, be absent in all of them for the following reasons: The factors leading to increased blood-pressure may be lacking; or the organism may be unable to respond to these factors; lastly, a once established hypertrophy may give way to later atrophy. The latter two features are important to remember, and have been fully demonstrated by our own records. The hypertrophy then occurs and persists only when the nutrition of the organ is kept up to the necessary standard.

Senator,[16] some years ago, pointed out that one could differentiate between two forms of hypertrophy: one with dilatation of the ventricle, the so-called eccentric; and one without dilatation, simple or concentric. He concluded from his observations the occurrence of the first in the large, degenerative, exudative, fatty, and hemorrhagic nephrites, while the latter was the rule in the small, contracted, productive forms. This view was soon opposed from many exceptions by Cohnheim and later observations, among which I have made a number myself. These demonstrated the dependence of eccentric or concentric hypertrophy upon the general nutrition of the individual. In the degenerative exudative nephrites with much œdema and hydrops, the nutrition of the individual and of the heart muscle, particularly toward the end, suffers severely; naturally, we find at autopsy dilated ventricles; on the other hand, in the slowly progressing uncomplicated productive nephritis, the nutrition usually remains very good till toward the end. Here concentric hypertrophy is therefore more frequently found. An absolute dependence of any form upon a particular kidney lesion does therefore not seem to exist.[17]

Now, how is this hypertrophy to be interpreted? Bright held to two possibilities: Either the heart is directly irritated by an abnormal composition of the blood, or this affects the finer and capillary vessels, thereby augmenting the work of the heart in order to drive blood through thus affected vascular districts.

The immediate successors of Bright in the study of renal disease did not further our knowledge regarding this matter, until the work of Traube[18] gave a new stimulus to it. Traube showed during life that within a few weeks after the occurrence of a severe nephritis symptoms appeared which pointed toward increased tension in the aortic system. These are abnormal resistance of the radials and the apex-beat, and an accentuated,

high-sounding, diastolic aortic and carotid tone. To them is added soon an increase in the heart volume, and Traube demonstrated in some cases hypertrophy of the heart in as short a time as four weeks after the beginning of a nephritis.

In this way he concluded a causal relation between nephritis and hypertrophy of the heart, and assumed for its explanation the following:

First: Inflammatory lesions of the kidney cause, by presence of an exudate or by loss of kidney substance, a diminution in the amount of fluid abstracted from the aortic system for the production of urine water. Second: They diminish the quality of blood which in a given time flows from the aortic to the venous system.

This purely mechanical hypothesis was soon attacked for physiological and pathological reasons. It was demonstrated by Cohnheim and Lichtheim [19] that a hydremic plethora has absolutely no influence on the blood-pressure, and by Ludwig and his pupils that even tying of both renal arteries had no appreciable effect on it. Furthermore, it is well known that, particularly in the productive nephrites, the amount of urine water is not only not diminished, but actually increased. Nevertheless, this mechanical theory was championed by Cohnheim in modified form, largely for the reason that experimentally and clinically left-sided hypertrophy follows total extirpation of one or gradual elimination of both kidneys, notably exemplified in cases of uncomplicated hydronephrosis. Lack of occurrence of hypertrophy under these conditions, and in amyloid kidney, was attributed by Cohnheim to purely nutritive disturbances. In order to meet the previously mentioned objections to Traube's theories, Cohnheim supposed that the rise in pressure was due, first, to entrance of an unchanged amount of blood into the kidneys, where it meets increased resistance, and, second, an

almost normal quantity of urinous substances, which determine, in his opinion, the degree of contractibility of the smaller renal vessels. In other words, Cohnheim believed that the amount of blood entering the smaller kidney arteries, whose contractive state is determined by the quantity of urinous substances, remains constant. Beyond these, however, it meets the increased resistance which necessarily leads to increase in general arterial tension.

This theory, like Traube's, has not enjoyed general recognition. Senator [20] has pointed out that the smaller kidney vessels are, as a rule, distinctly diseased, so that the conception advanced by Cohnheim seems unreasonable. For Krehl [21] and others it is impossible to understand how elimination of a relatively small area of circulation should be followed by such a permanent rise in general blood-pressure, and not by compensatory dilatation in other districts, a fact which is the rule in other conditions, finally there is no direct relation between the extent of hypertrophy and the degree of kidney contraction.

Schmidt,[22] who differentiates between two kinds of nephritis, glomerulonephritis and pure parenchymatous types, in which I am unable to follow him, believes that the affection of the glomeruli is of greatest importance in the rise in tension and ultimate hypertrophy, although intensity and generality of the glomerular lesions do not seem to have any relation. Schmidt believes, therefore, that the whole is a reflex process, acting, not on the heart directly, but on the smaller arteries. But, inasmuch as I have never seen any nephritis without glomerular lesions, I cannot support any of his contentions. But granting it, one cannot see why the blood-pressure is so extremely high in late stages of productive nephritis, when glomeruli have largely disappeared; and why much lower in the fatty degenerative type, where glomeruli are still persistent and generally diseased.

By far the largest number of investigators look for the cause of high tension and hypertrophy of the heart outside of the kidney. One group of ideas finds the explanation in changes of the arterial system. To them, rise in blood-pressure and hypertrophy of the heart is not dependent upon, but associated with, the nephritis. The ideas of Gull and Sutton, and others, on "arteriocapillary fibrosis," form the foundation for these views. We have previously studied the arterial changes in the kidney, and those of the other arteries outside of the kidney are very similar. Many, as we saw, are not the cause of, but actually dependent on, the rise of blood-pressure and the heart hypertrophy. Furthermore, the occurrence of arteriosclerosis in nephritis varies so much, and frequently in severe cases with much hypertrophy in the young is so conspicuously absent, that we cannot bring it in any essential relation to the hypertrophy. Some time ago the question of splanchnic arteriosclerosis as cause for high blood-pressure was much discussed. It was thought that, although the larger abdominal vessels might not show marked lesions, smaller arteries of the abdominal organs in spleen, liver, pancreas, gut, etc., presented sufficiently far-reaching arterial narrowing to account for rise of nephritic blood-pressure. I have paid some attention to this myself, but have been unable to trace any satisfactory relation between splanchnic arteriosclerosis and rise in blood-pressure.

Ewald[23] considered that an increased internal friction of the blood might account for the hypertrophy, but Hirsch and Beck[24] found the viscosity of the blood not increased in nephritis.

By far the largest number of investigators, and even Bright, have accepted one or the other chemical or toxic explanation of rise of blood-pressure with hypertrophy of the heart. We owe to Senator[25] an exceedingly well-formulated expression of this view, and the ideas of other investigators along these lines may

well be regarded as modifications of Senator's original conception. In the first place, he holds that somewhat different factors are potent in producing hypertrophy of the heart in various forms of nephritis. In what he terms "parenchymatous nephritis," and what we call degenerative exudative nephritis, the kidney and the whole organism are exposed to an irritant, which therefore acts on heart and blood-vessels as well as on kidneys, and produces primarily œdema. The latter process removes some of the toxic irritants from the circulation. If the lesion thus ameliorates, a necessarily somewhat weaker but persistent irritant continues a vasocontraction, followed by thickening of the vessels. Simultaneously, this irritant acts on the heart muscle. The heart muscle hypertrophies, therefore, for two reasons: First, as the result of an increased resistance; and, secondly, as the direct result of an irritant. These are the responsible factors, according to Senator, in what he terms the chronic parenchymatous and secondary contracted kidneys—conditions which we called degenerative exudative and degenerative productive nephrites. In the primary productive nephritis, on the other hand, the irritant, although constant, is never strong enough to lead to hydrops or œdema, but produces here also contraction of smaller arteries, which is necessarily followed by hypertrophy, particularly of the left ventricle. Under both conditions, then, a similar resulting increased pressure in the aortic system occurs: These ideas were actually supported by experimental observations which showed a transient rise in blood-pressure after injection of urea, although Senator himself is inclined to attribute an even greater influence to the other nitrogenous waste-products.

This theory is very ingenious, particularly as it accounts not only for the rise in blood-pressure and hypertrophy of the heart, but brings these at once in a relation with the œdema of nephritis.

As I told you, the main principles of this toxic theory have now been generally accepted. Krehl's idea, which is somewhat simpler, is that the contraction of the smaller arteries is the most important factor, and that this is not to be regarded as a spasm of these vessels, but rather as an increased tonicity of the normal vascular tone, which is probably under the influence of definite nervous vascular centers. A discussion of these clinical features of high blood-pressure will be found in T. C. Janeway's monograph on the subject.[18]

Against these ideas it was again urged by Cohnheim that they are dealing with hypothetical substances, about the existence and action of which we have neither proof nor any knowledge; and, secondly, that in the early stages of productive nephritis, when the secretion of solids and urine water is not only not diminished, but actively increased, the arterial tension is very high and the circulatory evidences appear frequently before any of the renal lesions become manifest. The retention of urinary products, to which Senator attributed the toxic vascular contraction, must, according to Cohnheim, be therefore out of question.

I, too, am of the opinion that in different forms of nephrites different factors enter into the production of rise in blood-pressure hypertrophy of the heart, and some of these are to be found outside of, and some within, the kidney. In the first place, it appears probable that in the early stages of productive nephritis a toxic factor must be of great issue. This, as evidence indicates, cannot be a retained normal urinary product, or products, for circulatory changes occur at an early date when retention of urine and solids is not only not diminished, but increased. It is, therefore, more probable to regard it as an abnormal either infective or metabolic poison, which increases, as Krehl suggests, the tonicity of all blood-vessels within and

outside of the kidney in permanent fashion, leading to rise in blood-pressure, hypertrophy of the heart, and a gradual waste of kidney substance. The whole process then—increased blood-pressure, hypertrophy of the heart, and nephritis—stands in correlation as the result of the injury of a foreign invasion and their effort to eliminate it from the system. Now, as the kidney substance wastes, certain new complicating factors are introduced on the part of the entirely changed circulatory conditions, and we may regard here, although modified from Traube and Cohnheim, a certain local influence. This has only lately been once more emphasized, so that I do not feel justified in denying it all importance, as some would have it.

We have, as Cohnheim held, anatomical observations which indicate that elimination of the circulation of the kidney is actually followed by hypertrophy of the heart, and further experimental work has again turned our attention to the ideas of Traube and Cohnheim. Thoma found, some time ago, in his experiments on the circulation in contracted kidneys, a very appreciable resistance within the kidney district, and Katzenstein has endeavored to prove that Cohnheim's reply to Ludwig's objection to Traube's theory was actually correct. Katzenstein[26] showed that, while Ludwig and his pupils were right in the observation that tying of both renal arteries outside of the kidneys, or at the hilus, was followed by no rise, but even a fall in blood-pressure, things differed when the resistance was introduced, while the renal circulation remained in connection with the aortic one. If the renal circulation was resumed after having tied the renal artery for a long enough time to obtain thrombosis in the vessels of the kidney, a very appreciable rise occurred and lasted several hours. These experiments corroborated some results previously recorded by Oscar Israel,[27] who obtained rise in blood-pressure after extirpation of both kidneys

in fifteen rabbits, and are perhaps less objectionable, because an influence of urinary substances cannot have been active.

It seems, therefore, that we cannot entirely dismiss the claims of Traube and Cohnheim that certain anatomical and experimental evidence points to the fact that resistance within the renal circulation may have an effect on general blood-pressure, and, therefore, if not the origin of high blood-pressure, contributing toward its maintenance.*

This factor, moreover, seems to account for the rise in blood-pressure which occurs in chronic venous congestion. In the various forms of degenerative and exudative nephrites, however, it is possible to conceive the coexistence of toxic and local conditions. In the later stages of these nephrites the waste of kidney substance, the new arrangement of the parts, elimination of glomeruli and other vascular channels within the kidney, may gradually add increasing momentum to the local factor, while the occurrence of uræmic manifestations, with sudden, sometimes tremendous, rises in blood-pressure, would indicate here also the persistence of the toxic influence, which, after considerable accumulation, suddenly rises to exert an overwhelming effect.

To these agents must finally be added, in some cases at least, a gradually increasing rigidity of all blood-vessels, which is attributable to the long-continued increase in their tonicity and their gradual thickening.

In this connection a few words about the relationship of the suprarenal glands to blood-pressure and hypertrophy of the heart: Recently some observers,[28] particularly among the French, have claimed that in long-continued nephrites with high

*The question whether this is due to a reflex or mechanical act is still unsettled. Professor Senator told me lately that in recent experiments he and others were unable to obtain this rise in blood-pressure if animals were deeply narcotized. This would argue, of course, against a mechanical factor.

blood-pressure a hyperplasia of the suprarenal medulla occurs, while the cortex also shows nodular, adenomatous hypertrophy. This is brought in relation to high blood-pressure as an expression of functional hyperactivity of these parts, mainly on the strength of the physiological experience that a blood-raising principle may be obtained from the medulla of the suprarenal gland, while a detoxicating power is ascribed to its cortex. It would lead me here too far to go into an elaborate discussion of the whole matter, but I would simply mention that we have been unable in this institute to corroborate these ideas, and, indeed, I should, from our experience, conclude that general atrophy of the cortex was a very prominent phenomenon in nephritis. The state of the suprarenal medulla varies so decidedly that it has not been possible for us to bring it into any relation to the nephritic process.

Of great importance are the changes in the serous membranes, not only on account of their practical interest, but because they throw some light on the genesis of œdema and hydrops, which we shall lastly have to consider.

It has been a common experience that nephritics are seriously threatened with inflammations of their serous membranes. Of these, it is particularly the pericardium; then, in order of frequency, the pleura, the peritoneum, and finally the meninges. So frequent is the combination of pericarditis and nephritis in our experience that when we find recent fibrinous or purulent pericarditis at autopsy, we immediately expect to disclose later a nephritis. The same holds true of fibrinous or purulent peritonitis, and it occasionally happens that such patients are operated upon, because during life an appendicitis or other localized peritoneal infection is suspected. This common involvement of the serous membranes was, as you will recall, known even to Bright and Christison. It is usually considered that the cause

for such terminal infections lies in the lessened resistance of the individual as the result of long-continued nephritic intoxications, but if we examine the matter carefully, and why particularly the serous membranes are thus so easily affected, we find that these have almost always been the seat of previous productive and atrophic inflammations. It is one of the commonest autopsy findings in nephritis to see the serous membranes in parts thickened, either diffuse, giving to the whole a white, shiny, pearly appearance, or only circumscribed; in others thin and wasted, deformed, adherent. Most interesting is the accompanying productive lymphangitis. The thickened, partly obliterated lymphatic vessels stand out very prominently in the form of pale, milky-white streaks, forming an irregular network, and, in places, accompanied by a perilymphangitis, become confluent to form smaller and larger patches.

These latter lesions are usually well accentuated and easily observed in the reflected visceral peritoneum, but can also be seen in pericardium, meninges, and pleura. From this experience it may be concluded that the productive inflammations of all serous membranes, which often become associated with serous, fibrinous, and even purulent exudations, are the result and expression of a general irritant to the lymphatic system in nephritis. It leads us directly to the causes of œdema and hydrops, a field which has for years been one of the most fruitful for experimental pathology.

For a full discussion of the early works and thoughts in the matter I refer you to the masterly presentation and criticisms of Cohnheim in the first volume of his lectures on general Pathology, Section VII, on Hydræmia and Anhydræmia. Recently the matter has been excellently discussed by Meltzer on the vitalistic, and Starling on the mechanical, side.[29] I shall, therefore, only emphasize certain points.

The oldest conceptions, now discarded as essential reasons for the production of œdema and hydrops, placed the hydræmic condition of the blood as foremost factor. It was thought that the gradual withdrawal of serum-albumin was followed by a thinning of the blood, and that this was easily permeable through blood-vessels. This idea, however, is in conflict with too many facts to be of essential consequence. Later, the hydræmia was ascribed to water-retention - a true hydræmic plethora. This latter was particularly championed by Bartels, who especially emphasized the inverse relation of diuresis, œdema, and hydrops. However, there are sufficient evidences to deny an essential rôle even to a hydræmic plethora, for the reason that, as Senator early pointed out, œdema appears frequently so early that the existence of hydræmic plethora may be ruled out with certainty, and that diminution in the amount of urine does not even lead to a hydræmic plethora. The most distinguished objection came here, again, from Cohnheim, who, with Lichtheim, produced experimentally in animals a hydræmic plethora of probably greater degree than is ever present in the human being. Such experiments were, however, never followed by anasarca. But if, on the other hand, irritative inflammatory conditions of the skin were produced, the œdema readily followed. For instance, if the femoral vein of a healthy dog was tied, no œdema occurred, yet if now a considerable amount of a sodium chlorid solution was infused, anasarca resulted. If, further, one of the hind paws of a dog was irritated so as to become inflamed, and cannulæ were inserted in the lymph-vessels of both legs, it was observed, after injection of a sufficient quantity of a solution of NaCl into the jugular vein, that decidedly more lymph dropped from the inflamed extremity, while the healthy side showed no appreciable change. The same occurred after the hydræmia was continued for several days. Cohnheim's conclusion was,

therefore, that intact vessels through which a normal blood-stream flows never give rise to œdema, that the latter is the result of a direct injury to, or nutritive disturbances in, the vessel-walls. These views found further corroboration in other observations. I may only recall to your mind that certain drugs, like arsenic, of which a direct injury to vessels is assumed, lead to the production of œdema. Magnus,[30] finally, has extended the early observations of Cohnheim and Lichtheim, and showed the susceptibility of the blood-vessels to a number of substances, among them the retained normal urinary products.

Of greatest interest and support here is also the direct evidence furnished by certain forms of nephritis in which we can easily recognize marked injury to vessels. This, as you recall, is particularly the case in scarlatinal nephritis. In scarlet fever the blood-vessels, not only of the kidney and throughout the whole body, but of the skin, are in decidedly irritated condition, and œdema is one of the most prominent symptoms. Senator, therefore, extending these views of Cohnheim, speaks of the nephritic hydrops as a "hydrops irritativus." We could easily quote more evidence, particularly of an experimental nature, to support the view that the condition of the blood-vessels—in other words, the toxic action of some irritant upon them, whereby their permeability is increased—is of paramount importance in the production of nephritic œdema.[31] I will desist from doing it because evidence is here so strong that we accept it; but the question remains whether it is the all-important and only factor in this matter. This possibility must be denied. For, as we know, increased transudation is by no means identical with œdema. In order to obtain the latter there must be added an interference with the lymph-flow. This, however, depends, as you recall from your physiological studies, upon the pressure difference in the capillary and lymphatic systems. The pressure

in the lymphatics is partly dependent upon the blood-pressure and, as Landerer[32] has shown, the tissue tension of the surrounding structures. Magnus and Krehl[33] have pointed out that these may very well be involved in nephrites. But, unfortunately, we have as yet no reliable data about the tissue tension in nephritis. It seems, nevertheless, very possible that the same toxic substances which injure vessels, injure tissue elasticity, either directly or by high osmotic pressure with water retention. You recall these views as familiar.

But it seems that the changes which take place in the lymphatic apparatus, and with which I made you acquainted a few moments ago, have not received adequate attention in their relation to the production of œdema. These indicate that there must also be a decided interference with lymph resorption and lymph motion, for it can certainly not be conceived how lymphatics which display so prominently the effect of irritative influence on the form of productive and obliterative lymphangitis and perilymphangitis can continue their normal functions; and, as a matter of fact, they would be called upon, under the previously outlined conditions, to do increased duty.

I am inclined, indeed, to regard the changes in lymphatics, for which we have anatomical foundations, as very essential for the production of any pathological transudate, as not even Cohnheim could produce œdema after injury to the vessel-wall unless the blood was hydræmic. In nephritis, however, it frequently occurs before hydræmia has developed. The lymphatics have usually been given a very subordinate position in the relation to œdema, mainly on the ground of certain evidence which has demonstrated extensive anastomosis among them. Obstruction of even large lymphatic vessels is, therefore, usually not followed by any accumulation of lymph and production of œdema. But these facts are hardly applicable to the question

of œdema in nephritis, for the reason that we are not only dealing with a localized, mechanical, lymphatic interference, which may be adjusted by compensatory action of healthy neighboring lymphatics, but with a general irritative condition which involves all the tissue lymphatics.

If we finally take into account the chemical changes which occur during certain nephrites, and to which some of the French investigators have attributed much influence, we can readily see how they may add to the ease with which blood-serum passes through injured vessel-walls. It has been demonstrated, for instance, that retention of NaCl has at times considerable influence on the production of œdema; but this has been found variable, inconstant, and therefore is in all probability not an essential, but a contributory, factor. To the same contributory category would belong hydræmia and venous stasis.

To sum up: The œdema of nephritis depends primarily on an output of serum through injured capillary districts, which cannot be removed on account of similar injury to the lymphatics and probably the surrounding tissues. Later in the disease metabolic and mechanical circulatory disturbances as well as retention may alter the composition of the blood and the vessel-walls to favor further the passage of watery elements through the capillary system.

The term "transudate" is, therefore, not strictly correct to apply to the nephritic œdema, and we may properly follow Senator's precedent and speak of an "œdema and hydrops irritativus," which at once brings these in the close relation to the exudative inflammations of serous membranes with which, as our experience taught us, they so frequently complicate and terminate.

We have traced, therefore, nephritis, increased blood-pressure, hypertrophy of the heart, anasarca, hydrops, and finally the

terminating inflammations of the serous membranes to a genetic relation.

And now a parting word, or, better, a suggestion from the pathological anatomist to you as clinicians, on the symptoms of nephritis and their relation to the nephritic process. I do not mean to tire you by a detailed discussion of these symptoms, which must be left to some competent clinical exposition, but I hope I have impressed upon you during these lectures that no nephritic process is an independent lesion of the kidney. For it depends, in an essential degree, upon concomitant and correlated changes outside of the kidney. This is so much the case that these acquire here an importance almost unparalleled in the diseases of other organs. We saw in the study of the anatomical features that we must sharply separate the results of the inflammatory changes in the kidney from those which occur as the results introduced by disturbances from outside. Similarly, in the symptomatology of nephritis you will find that the complex clinical pictures of the various types may be separated into two great groups of symptoms—the renal and extrarenal. The importance of those in individual cases, as you can readily see, varies constantly. In the early stages of slowly progressing productive nephrites, for instance, the extrarenal symptoms are of much greater value and importance than the renal, for the kidney is still sufficient, and, if anything, hyperfunctionates. Not until much later occur the superadded evidences of the serious renal involvement. Vice versâ in some of the rapidly developing exudative degenerative types, the symptoms of the renal affection may dominate from the start, and later become modified by the extrarenal changes. Herein lies a great difficulty in the study of renal inflammations. And if this offers, as I pointed out at the beginning of these lectures, great obstacles on the anatomical side, they are necessarily much

greater on the clinical. We may find in this also the cause for the occasional conflict between the views of the pathological anatomist and the clinician. The latter classifies necessarily largely according to certain groups of symptoms and well-established functional disturbances, which represent the sum total of the interferences produced by a disease in the relation of all viscera to each other. The former classifies the changes in one organ according to their pathogenesis, and endeavors to analyze them in more or less abstract independence.

We have arrived at the end. Perhaps my presentation of the subject has seemed very old-fashioned to you. It perhaps has been discussed too much for your tastes in well-trodden paths, or it has not acquainted you with new, startling ideas. But, after all, it may be that one or other part of the discussion has aroused your own thought and reason to go further than what was here presented, and you may feel more encouraged in this effort if I remind you of a remark Goethe once made: "Alles in der Welt ist schon einmal gedacht worden, es ist nur nöthig es noch einmal zu denken."

NOTES AND REFERENCES

The literature on Bright's disease is so enormous, and of late years so much, particularly experimental, work has accumulated, that it has been perfectly impossible to even mention all the important contributions to the various phases of the subject. Omissions will, therefore, be found frequent, and much valuable material may have escaped my notice. These lectures were not intended as an exhaustive treatise on the subject, but to familiarize the hearer, and now the reader, with the fundamental facts and to give him a base for own thought and research. The notes and references are, therefore, no exhaustive record of the literature, but intended to supply to the reader, not only corroboration of quotations, but to open a particular field which he may wish to pursue further.

FIRST LECTURE

1. Ætii medici græci contractæ ex veteribus medicinæ tetrabibli sive quaternionis tertii. Lugduni MDXLIX.
   Sermo secundus et ex ordine decimus. Cap. xx. De hydrope sive aqua inter cutem.
   Sermo tertius et ex ordine unidecimus. Cap. xvi. De renum inflammatione.
   Avicennæ arabum medicorum principis, etc. Venetiis MDCVIII Apud Juntas. Tom i. Fen ii. Doctrina 3. De significantibus coloris urinæ.
2. Before Morgagni similar observations were recorded by Bonetus in his well-known Sepulchretum anatomicum, ed. Mangeti, Lugduni MDCC, Lib. iii, sect. xx, observ. xvi, and later by J. Lieutand, Historia anatomico-medica, etc., E. Portal, Paris, 1767, i. Portal, Cours anat. medicale. Schenck, Observat. med. rar., lib. vii. Morgagni, De sedibus et causis morborum per anatomem indagatis, 1761. Epist. xxxviii, xl, and xlii. In the beginning of the 42d epistle the history of the knight, quoted from Valsalva, will be found particularly interesting, not only from the pathological standpoint, but as a contribution to the social conditions of the times.
3. Cotunii: De ischiade nervosa commentarius. Viennæ, 1770, p. 24.
4. In Rollo: Diabetes mellitus. Chapter vi, London, 1798.
5. Observations on Dropsy, which Succeeds Scarlet Fever. Transactions of Society for the Improvement of Medical and Chirurgical Knowledge, vol. iii.

6. Brande: An Account of Some Changes from Disease in the Composition of Human Urine, London, 1807. Scudamore: A Treatise on the Nature of Gout, London, 1823, page 313.
7. Bright: Reports of Medical Cases, i, 1827; ii, 1831.
8. Cases and Observations Illustrative of Renal Disease, Accompanied with the Secretion of Albuminous Urine, by Dr. Bright, Guy's Hospital Reports, vol. i, MDCCCXXXVI. I reproduce here his excellent description of the clinical history of the disease for those who are unable to consult the original on pp. 339, 340, and 341:

"A child, or an adult, is affected with scarlatina, or some other acute disease; or had indulged in the intemperate use of ardent spirits for a series of months or years; he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands œdematous. If he happen, in this condition, to fall under the care of a practitioner who suspects the nature of his disease, it is found that already his urine contains a notable quantity of albumin. His pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of pain or weight across the loins. Under treatment more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to micturition disturb the night's repose. After a time, the healthy color of the countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, of weariness, and of depression, gradually steal over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested; and found, in almost every trial, to contain albumin, while the quantity of urea is gradually diminishing. If, in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serum is milky and opaque; and nice analysis will frequently detect, a great deficiency of albumin, and sometimes manifest indications of the presence of urea. If the disease is not suspected, the liver, the stomach or the brain divide the care of the practitioner, sometimes

drawing him away altogether from the more important seat of disease. The swelling increases and decreases; the mind grows cheerful or is sad; the secretions of the kidney or the skin are augmented or diminished, sometimes in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health; again he enters on his active duties: Or he is, perhaps, less fortunate;—the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become œdematous and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrences of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged; his vision indistinct; his hearing depraved; he is suddenly seized with a convulsive fit, and becomes blind. He struggles through the attack; but again and again it returns; and before a day or a week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed."

9. Christison: Observations on the Variety of Dropsy which Depends upon Diseased Kidneys, Edinburgh Medical and Surgical Journal, vol. xxxii, 1829. And, On Granular Degeneration of the Kidney, Edinburgh, 1839.
   Osborne: On Dropsies Connected with Suppressed Perspiration and Coagulable Urine, London, 1838; and, On the Nature and Treatment of Dropsies; Dublin Journal of Medical and Surgical Sciences, 1834.
   Gregory: Edinburgh Medical and Surgical Journal, xxxvi, p. 315, and xxxvii, p. 54.
10. London Medical Gazette, vii, 1831.
11. Dictionary of Practical Medicine; under Dropsy.
12. Dublin Journal of Medical Sciences, 1833, 16.
13. Urinary Diseases and Their Treatment, London, 1838.
14. Rayer: Traité des maladies des reins, Paris, 1840.
15. Tissot: De l'hydropsie causée par l'affection granuleuse des reins, Paris, 1833.
16. Sabatier: Considérations et observations sur l'hydropsies symptomatique d'une lésion spéciale des reins. Archive générale de médecine. Sec. ii.

17. Désir: De la présence de l'albumine dans l'urine, considérée comme phénomène et comme signe dans les maladies. Paris, 1835.
18. Genest: État actuel des connaissances sur la maladie des reins désignée sous les dénominations de maladie de Bright, affection granuleuse, néphrite albumineuse. Gaz. méd. de Paris, 1836, p. 449.
19. M. Solon: De l'albuminurie ou hydropsie causée par une maladie des reins. Paris, 1838.
20. Becquerel: Séméiotique des urines, ou Traité des altérations de l'urine dans les maladies, etc. Paris, 1841.
21. In Casper's Wochenschrift, 38, 39, 40, 1839. And, Anatomische und mikroskopische Untersuchungen zur allgemeinen und speciellen Pathologie, 1838. Later: Abhandlungen zur Physiologie und Pathologie, Jena, 1842.
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23. De renibus in morbo Brightii degeneratis. Dissert. inaug. Berol. 1839.
24. Zeitschrift für rationelle Medizin, 1841, i, p. 67; ii, p. 220, and Handbuch der rationellen Pathologie, ii, 1847, p. 303 ff.
25. De morbo Brightii, Erlangal, 1844.
26. Johnson: Medico-Chirurgical Transactions, xxix, xxx, xxxii. Also, The Diseases of the Kidney, and Lectures on Bright's Disease.
27. Medico-Chirurgical Transactions, xxix, p. 318.
28. Ibid., xxx.
29. Ibid., xxx.
30. Charité Annalen, i, 1850.
31. Frerichs: Die Bright'sche Nieren Krankheit, etc. Braunschweig, 1851.
32. Rockitansky: Lehrbuch der pathologischen Anatomie, ii.
33. Ueber parenchymatöse Entzündung, iv, p. 261. (Classic. Should be read by everybody.)
34. Die Bindesubstanz der Niere im gesunden und kranken Zustande. Berlin, 1859.
35. Cohnheim's work on inflammation is to be consulted in his Vorlesungen über allgemeine Pathologie; on the kidneys he followed mainly Weigert's views. Ibid.
36. Traube's views are presented in: Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, 1856; Deutsche Klinik, 1859, 31–32; Allgemeine med. Centralzeitung, 1856, 65; Deutsche Klinik, 1863.
37. Klebs: Lehrbuch der pathologische Anatomie, 1876, i, 144.
38. Nephritis und Albuminurie, Bonn, 1881.
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40. Verhandlungen des Congresses für innere Medizin. Erster Congress, 1882.
41. Guy's Hospital Reports, viii, 1852, 2d series.

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43. Medico-Chirurgical Transactions, lv, 1872.
44. Volkmann's Sammlung klinischer Vorträge, 1871, 35, and v. Ziemssen's Handbuch der spec. Pathol., ix, 1, 1875 and 1877.
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46. Die Bright'sche Nierenkrankheit vom pathologisch-anatomischen Standpunkt. Volkmann's Sammlung klinischer Vorträge, 1879, Nos. 162 und 163. (An exceedingly important work.)
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48. Beiträge zur Kenntniss des Morbus Brightii, Ziegler's Beiträge, Jena, 1886, i.
49. Loc. cit.
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51. Virchow's Archiv, xix, 1860.
52. Archiv für Heilkunde, 1867.
53. Handbuch der pathologischen Anatomie, vol. i, 1876.
54. Journal of Experimental Medicine, 1898, iii.
55. Lehrbuch der speciellen pathologischen Anatomie, 1893, ii.
56. Loc. cit., page 47.
57. Loc. cit., page 190 ff.
58. Verhandlungen der deutschen pathologischen Gesellschaft, Jahrgang 1905, p. 64.
59. Ueber die entzündlichen Veränderungen der Glomeruli. Arbeiten aus dem pathologischen Institut zu Leipzig, 1907, monograph.
60. Studies in Pathological Anatomy, Acute and Chronic Bright's Disease.

SECOND LECTURE

1. Consult: Schäfer's Histology, Böhm and Davidoff's Text-book of Histology, and Stöhr's Text-book of Histology. Also Landois and Sterling's Physiology, where histological and physiological problems are discussed. Also Frerich's Die Bright'sche Nierenkrankheit, 1851; Krehl, Pathologische Physiologie; and Oswald, Lehrbuch der chemischen Pathologie (Harnabsonderung).
2. The Development of the Malpighian Bodies of the Kidney, etc., Journal of Pathology and Bacteriology, 1900, vi, p. 459.
3. Consult here particularly Starling on the secretion of urine in Schäfer's Text-book on Physiology, vol. i, and Hermann's Lehrbuch der Physiologie. The former, particularly, gives a readable presentation of the whole subject.
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c. Ludwig, ibid., Bd. 48, ii (1883).
c. Ludwig, Wagner's Handwörterbuch, ii, 637.
6. Ribbert: Virchow's Archiv, Bd. xciii, 169. After removal of the renal medulla in rabbits Ribbert observed a very abundant secretion of thin urine. These experiments are open to objection, as Munk and Senator point out. Loc. cit., p. 23, foot-note; and, further, Boyd, Journal of Physiology, vol. xxviii, 1902. The later evidence: Hans Meyer, Ueber Diurese. Sitzungsberichte d. Gesellschaft zur Beförderung der gesammten Naturwissenschaften. Marburg, 1902, p. 92 ff. Cushny, Journal of Physiology, 1902, vol. xxvii.
7. Cited after Starling, Mechanism of the Secretion of Urine, in Schäfer's Text-book of Physiology, vol. i. Pfeffer, Osmotische Untersuchungen, Leipzig, 1877. Dreser, Archiv für experimentelle Pathologie und Pharmakologie, 1892, xxix, 307.
8. Verhandlungen der Deutschen pathologischen Gesellschaft. Jahrgang 1905. Morbus Brightii, p. 64 ff.
9. Breslauer ärztliche Zeitschrift, 1879, 22, and extensive discussion in Hermann's Handbuch der Physiologie, v. i, pp. 309.
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11. Sobieranski: Archiv für exp. Path. u. Pharm., xxxv, 144.
12. Senator: Die Albuminurie, 1882, gives a full discussion of this subject and further references. Also, Verhandlungen der Berliner Physiol. Gesellschaft, Dec. 16, 1881, in Du Bois Réymond's Archiv, 1881, and Berliner klin. Wochenschrift, 1885.
13. Munk and Senator: Zur Kenntniss der Nierenfunktion, etc., Virchow's Archiv, 114, p. 1, 1888. Senator, Ueber Transudation, Virchow's Archiv, 111, S. 219.
14. Fr. Müller: Loc. cit.
15. Loc. cit.
16. Archiv für experimentelle Pathologie und Pharmakologie, vols. xlviii and l.
17. Gottlieb und Magnus: Ibid., vol. 45.
18. Hofmeister's Beiträge, ii, 1902.
19. Ibid., ii, 1902.
20. Ueber Diabetes insipidus und andere Polyurien. Deutsches Archiv für klinische Medizin, 1905, vol. 83, p. 67 ff. (Quotes the other literature.)
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23. Zeitschrift für klinische Medizin, 33, i, 1897; 34, i, 1898.

THIRD LECTURE

General reference works on nephritis and allied subjects:

Senator: Die Erkrankungen der Nieren. Wien, 1902. Alfred Holder. (Quotes literature extensively. Very good historical introduction.)

Kaufmann: Lehrbuch der speciellen pathologischen Anatomie, Berlin, 1907. Georg Reimer. (Excellent for reference and literature.)

Ziegler: Allgemeine Pathologie und pathologische Anatomie, Band 2, Jena, 1906. Gustav Fischer. (Literature.)

Cohnheim: Vorlesungen über allgemeine Pathologie, Berlin, 1880. August Hirschwald, Zweiter Band.

Krehl: Pathologische Physiologie, Leipzig, 1907. 5th Auflage. F. C. W. Vogel. (Particularly for the functional changes.)

Orth: Lehrbuch der speciellen pathologischen Anatomie, II. Band, 1. Abteilung, Berlin, 1893. A. Hirschwald. (Literature.)

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Aschoff: Lehrbuch der pathologischen Anatomie, II. Bd. Jena, Fischer, 1909.

Hoche et Briquel: Les Lesions du Rein, Paris, 1904. (With good atlas.)

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3. Ibid., p. 241.
4. Ibid., p. 200.
5. Cellular Pathologie, Berlin, 4. Aufl., 1871.
6. Die Lehre von der trüben Schwellung, Preisschrift, Würzburg, 1891.
7. Virchow's Archiv, cxlix, p. 401.
8. Elemente der Pathologie, 3. Aufl., 1896.
9. Vorlesungen über allgemeine Pathologie, 1882.
10. Allgemeine Pathologie, 1889.
11. Lehrbuch der allgemeinen Pathologie.
12. Lehrbuch der allgemeinen pathologischen Anatomie.
13. Lehrbuch der pathologischen Anatomie.
14. Handbuch der allgemeinen Pathologie.
15. Virchow's Archiv, cxxxv, p. 470.
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18. Verhandlungen der deutschen pathologischen Gesellschaft, 1900.
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23. Beer: Loc. cit.
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25. Archivio per le szienze mediche, 1883, vi, 3. Sulla hypertrofia compensatoria dei reni; and Neoformazione dell'epitelio dei canaliculi oriniferi della malatta di Bright. Ibid., 1884, viii.
26. Thorel: Ueber typische und Pseudoregeneration bei Niereninfarkten, Virchow's Archiv, 146, 1896.
Rössle: Störungen der Regeneration von Nierenepithelien. Virchow's Archiv, 170, 1902.
Jatta: Sulla regenerazione dell'epitelio del rene. Archivio per scienze mediche, xxiii, p. 323.
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28. Ueber Tuberkel und Tuberkulose, Zeitschrift für klinische Medizin, ix–x.
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30. Loc. cit.
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37. Inflammatory Changes in the Kidney, etc., Journal of Pathology and Bacteriology, July, 1904.
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41. Loc. cit. and Die normale und pathologische Anatomie und Physiologie

der Niere. Bibliotheca medica C. H. and Bildung der hyalinen Zylinder. Centralblatt f. allg. Path., iv, 1893.

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44. Granulabildung bei Nierenentzündung, Ziegler's Beiträge, vii, Supplement, 1905.
45. Israel: Virchow's Archiv, cxxiii.
    Ernst: Fibrin in hyalinen Zylindern; Ziegler's Beiträge, xiii, 1893.
46. Natur und Entstehung der Nieren Zylinder, Centralblatt für allg. Pathol., iv, 1893.
47. Loc. cit.
48. Zeitschrift für klinische Medizin, i, 1879. Centralblatt für die mediz. Wissenschaften, 1880. Singer: Zeitschrift für Heilkunde, vi, 1885. Cohnheim also held to this possibility.
49. Virchow's Archiv, lxxvi.
50. Posner (Virchow's Archiv, lxxix) looks upon most casts as coagulated transuded or exuded albumin, and derives the coagulating ferment from the disintegration of the leukocytes. Similar were Weigert's views (Virchow's Arch., lxxii, p. 254).
51. Loc. cit., Journal of Exp. Medicine.
52. Ueber Fettinfiltration und fettige Degeneration d. Nieren, Virchow's Archiv, 180, 1905.

FOURTH LECTURE

1. The observations of Petrone (1881) and Pisenti (1884) on the new formation of glomeruli and new tubules have generally been rejected by later investigators.
2. Loc. cit., p. 99.
3. Loc. cit.
4. Zur Entwicklungsgeschichte des Krebses nebst Bemerkungen über Fettbildung im thierischen Körper und pathologische Resorption. Virchow's Archiv, i, p. 94, 1847.
5. Pettenkofer and Voit, in Liebig's Annalen, Supp. ii, 361, Zeitschrift für Biologie, vi, 277 (1870); vii, 433 (1871). Bauer: Zeitschrift f. Biologie, vii.
6. Die Entstehung von Fett aus Eiweiss, etc. Pflüger's Archiv, 77, 1899.
7. Gibt es eine fettige Degeneration? Verhandlungen des 15ten Kongresses für innere Medizin, 1897. And, Ueber Fettwanderung Verhandlungen des 13te Kongresses f. inn. Med., 1895.
8. Ueber Fettgehalt des Blutes u. einiger Organe des Menschen, Virchow's Archiv, 174, 1903.

9. Ueber Fettansatz im Thierkörper, Med. Zentralblatt, 8, 1882. And, Pflüger's Archiv, 31, 11, 1883.
10. Ray, MacDermott and Lusk, American Journal of Physiology, 1899, iii. Lusk and Mandel, Lactic Acid in Intermediary Metabolism, ibid., 1906, xvi. Lusk, Metabolism in Phosphorus-poisoning, ibid., 1907, xix. Lusk, The Elements of the Science of Nutrition, 1906. Saunders.
11. Ueber experimentell erzeugte Fettsynthese, etc., Virchow's Archiv, 174, 1903.
12. Literature on autolysis: Umber, Die Klinisch-pathologische Bedeutung der Autolyse, Berliner klinische Wochenschrift, 1903, xi, 185. Opie, Journal of Exp. Med., 1905, vii, p. 316, 759. Flexner, Note on Autolysis in Lobar and Unresolved Pneumonia. Transactions of Association of American Physicians, 1903, xviii, 1359. Waldvogel, Autolyse und fettige Degeneration, Virchow's Archiv, 1904, 175, i. Phosphorvergiftung und Autolyse, Deutsches Archiv f. klin. Medizin, 1905, 82, 437. F. Müller, Pathologie des Stoffwechsels. Levene, P. A.: Autolysis, Harvey Lectures, N. Y., 1905–1906, Lippincott Co.
13. An excellent Discussion in Adami's address before the New York Harvey Society on Myelins, etc., published in the Harvey Lectures for 1906 to 1907, New York, Lippincott Co. For the chemistry see Hammersten, Physiologische Chemie, translated into English by J. Mandel. Also, Hoppe-Seyler's Physiologisch und pathologisch chemische Analyse. Aschoff, Ziegler's Beiträge, Bd. 47, i, p. 7, gives the most recent and extensive discussion.
14. Oertel: Beiträge zur Kenntniss der Ausscheidung des organischgebundnen Phosphors im Harn, Zeitschrift f. physiol. Chemie, xxvl. Keller, ibid., xxix. Matthison, Biochemical Journal, iv, 5, 6, and 7. Mandel and Oertel, N. Y. University Bulletin of Medical Sciences, i, p. 165, 1901.
15. Symmers: Journal of Pathology and Bacteriology, vol. x, 1905, p. 159 ff. and p. 427 ff.
16. See Hammersten, Lehrbuch der physiologischen Chemie, 1907, p. 338.
17. Ueber Fettinfiltration, etc., Virchow's Archiv, 180, 1905. Also, Orgler, Ueber das Auftreten von Myelin in Zellen, etc., Virchow's Archiv, 167, 1902.
18. See Stoerck, Ueber Protagon und über die grosse weisse Niere. Sitzungsberichte der K. Akademie der Wissenschaften, Math.-nat. Klasse, Wien, 115, 1896. Kaufman, Specielle pathologische Anatomie, 1907, pp. 787–788.
19. See Kraus, Ueber Fettdegeneration und Fettinfiltration. Verhandlungen

der Deutschen pathologischen Gesellschaft, sechste Tagung, 1904, p. 37 ff.

20. On the Large White or Soapy Kidney. Journal of Medical Research, Boston, xx, p. 27.
21. Loc. cit.
22. Loc. cit.
23. Ueber den Lecithingehalt des Herzens u. der Nieren, etc., Arch. f. exp. Pathologie und Pharmakologie, 52, 178, 1905.
24. Lehrbuch d. chemische Pathologie, 1907. Has a review of the subject of fat degeneration and fat infiltration.
25. Wichman: Die Amyloiderkrankung. Beiträge von Ziegler, xiii, 1893; and Martland, in Medical and Surgical Reports of New York City Hospital for 1908. Hueter, Centralblatt für Pathologie, Bd. xix, 23, p. 961.
26. Herxheimer: Hyaline Degeneration der Glomeruli der Niere, Ziegler's Beiträge, Bd. 45, 1909.
27. Histology of Liver Tissue Regeneration. Journal of Pathology and Bacteriology, xiii, p. 127.
28. Verhandlungen der deutschen pathologischen Gesellschaft, 1905. Ueber Morbus Brightii.
29. Herxheimer and Hall: Ueber die Entkapselung der Niere, Virchow's Archiv, 179, 1905, discuss this matter fully and also give the literature.
30. Ueber den Ausgang der cyanotischen Induration der Niere in Granularatrophie. Wiesbaden, 1893.

FIFTH LECTURE

1. Fr. Müller: Loc. cit., p. 99.
2. Kaufmann: Lehrbuch der pathologischen Anatomie.
3. Zur Kenntniss der Circulationstörungen in den Nieren bei chronischer interstitieller Nephritis, Virchow's Archiv, Bd. 71, p. 42.
4. Ueber die punktformigen Kalkkörperchen, etc., Virchow's Archiv, Bd. 162, p. 85.
5. The literature on arteriosclerosis is very extensive. The following will be found useful for reference: Jores, Wesen und Entwicklung der Arteriosklerose, Wiesbaden, 1903; Marchand, Ueber Arteriosklerose, Kongress für innere Medizin, Leipzig, 1904. A somewhat different stand is taken by Adami; see his paper in the October number of the American Journal of the Medical Sciences, 1909, "The Nature of the Arteriosclerotic Process," which also covers Klotz's work.
6. Loc. cit. and Ueber die Arteriosklerose der kleinen Organarterien, und ihre Beziehungen zur Nephritis, Virchow's Archiv, 178. Hypertrophie und Arteriosklerose der Nierenarterien, ibid., 181.

7. Prym: Ueber die Veränderungen der arteriellen Gefässe bei interstitieller Nephritis, Virchow's Archiv, Bd. 177.
8. Ueber chronische Nephritis und ihre Beziehung zur Arteriosklerose, Virchow's Archiv, Bd. 195.
9. Thoma's views may be found in Virchow's Archiv, Bd. 93, 95, 104, 105, 106. Also, Ueber senile Veränderungen des menschlichen Körpers, Leipzig, 1884.
10. Ueber die Veränderungen kleiner Gefässe bei Morbus Brightii, etc., Virchow's Archiv, Bd. 71.
11. Ueber die Veränderungen der kleinen Arterien bei Nierenerkrankungen, Virchow's Archiv, 159, 1900. And, reply to Jores, Virchow's Archiv, Bd. 180.
12. Ueber Schrumpfniere ohne Arteriosklerose. Virchow's Arch., 180.
13. Loc. cit.
14. Kretz (Ueber Lebercirrhose. Wiener klinische Wochenschrift, 2, 1900.) Similarly, has shown an entirely changed regenerative reconstruction in the architecture of the liver in cirrhoses.
15. Consult here the presentation of Krehl, Pathologische Physiologie, Leipzig, 1907, pp. 33 ff. (Literature.) And, Senator, Die Erkrankungen der Nieren, p. 110 ff.
16. Virchow's Archiv, lxxiii, 1878.
17. Senator still holds these views on the ground of clinical evidence, which he considers here stronger and more conclusive than the anatomical.
18. Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, 1856. And, Nachträgliche Bemerkungen dazu in Deutsche Klinik, 1859, 31 and 32. An excellent modern presentation of the whole subject of blood-pressure in T. C. Janeway's monograph, "The Clinical Study of Blood-pressure."
19. Cohnheim: Allgemeine Pathologie, vol. ii, 2te Aufl., pp. 258 and 361.
20. Loc. cit., 1902, p. 122.
21. Pathologische Physiologie, p. 38, etc.
22. Verhandlungen der Deutschen pathologischen Gesellschaft, 1905. (In the general discussion on Bright's disease.)
23. Du Bois Réymond's Archiv, 1877.
24. Hirsch and Beck: Archiv f. klinische Medizin, 69, 503, and 72, 560. Archiv für experimentelle Pathol., etc., 54. (Cited by Krehl.)
25. Loc. cit., p. 125. Virchow's Archiv, lxxiii, 1878.
26. Experimenteller Beitrag zur Erkenntniss der bei Nephritis auftretenden Hypertrophie des linken Herzens, Virchow's Archiv, 182, p. 327.
27. Virchow's Archiv, 86, p. 295.
28. Consult Pearce, in the Journal of Experimental Medicine, x, 1909, p. 735 ff.

29. Meltzer: Lectures on Œdema. American Medicine, 1904, 1, 2, 4, and 5. Starling: Lectures. Lancet, 1906, May 9, 16, 23. See also: Adami, Principles of Pathology, ii, p. 103 ff.
30. Archiv für experimentelle Pathologie, etc., 42.
31. Important in this connection are the observations made in experimental nephritis induced with chromium and uranium salts. Chromium and uranium both produce a nephritis, which, however, in the former is unaccompanied by œdema, while the latter is associated with extensive œdema. Heineke, moreover, has found that the serum of animals poisoned with uranium has the property of producing œdema in other animals. Similarly, it has been shown by Kast and Starling that the blood-serum of œdematous nephritics causes increased lymph-flow in animals. See also, Pearce, Archives of Internal Medicine, iii, 1909, p. 422.
32. Die Gewebespannung. Leipzig, 1884.
33. Krehl, loc. cit., p. 123, with further literature.

APPENDIX

Classification of Nephritis

I. *Nephritis simplex:* Cloudy swelling, inflammatory œdema, and serous exudate.

Nephritis prolifera: Characterized particularly by inflammatory proliferation of parenchyma cells.

II. *Nephritis degenerativa et exudativa:* Marked degenerations and necrosis of fixed cells, and cellular exudate into glomeruli, periglomerular and intertubular tissue. Inflammatory proliferation of epithelium. Cast formation. Frequently hemorrhages and proliferation of fixed cells.

III. *Nephritis degenerativa et productiva:* The exudative features in the background. The degenerative (particularly fatty) changes prominent; cast formation; proliferation of epithelium and formation of epithelial giant-cells; gradual collapse and loss of kidney substance; appearance of leukocytoid and fibroblastic cells in the interstitial tissue, with the gradual formation of mature fibrous tissue, first patchy, then more diffuse. Hemorrhages occasionally present. Gradual thickening of blood-vessels, with occasional infarcts.

IV. *Nephritis productiva:* Gradual, first patchy, then more diffuse, inflammatory obliteration of renal parenchyma, leading to general, particularly cortical, loss of kidney substance. Abundant overgrowth of fibrous connective tissue. Gradual change in the types of secretory epithelium. Marked thickening of blood-vessels, with eventual narrowing of lumen and obliteration. As the result of these, infarct formation with healing by scar tissue.

Non-inflammatory Lesions of the Kidney, Occasionally, but Wrongly, Grouped as Nephritis

I. *Induratio cyanotica renum:* The cyanotic induration of the kidneys resulting from nutritive disturbances as the result of long-continued venous stasis. Congestion of all vascular districts, taking origin and remaining marked particularly in the medulla; accentuation of

all markings followed by œdematous imbibition of the parts; localized atrophy and collapse of kidney substance with equally localized fibrous tissue growth. Secondary changes in blood-pigment, due to hemolysis and setting free of clumps of blood-pigment.

II. *Atrophia vel sclerosis renum:* The senile atrophy and sclerosis of the kidney. Slight and patchy, to extreme and general atrophy and obliteration of renal parenchyma, with marked arteriosclerosis, obliteration of vessels, and infarctions. Dilatation of renal pelvis with marked breaking up or loss of its elastic muscular layer. Frequently additional stasis with œdema. In certain cases the arteriosclerotic changes much less prominent, infarctions, therefore, lacking, and the kidney presents a simple diminution in size, with relatively smooth surface.

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